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EDITOR ERIK LINDGREN

THERAPY PHYSICS BIOLOGY

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SVEN HULTBERG

in

Memoriam

Professor Sven Hultberg of Karolinska Sjukhuset and Director of Radiumhemmet died of coronary thrombosis on April 24 1965 at the age of 57 He received his medical education at Lund University and graduated in 1943 with a thesis on short range radiation in the treatment of superficial skin and lip cancer In the same year he was appointed assistant professor at Radiumhemmet where for seven years he worked directly under Professor Elis Berven When Hugo Ahlbom who succeeded Elis Berven in 1950 died after only a few years Sven Hultberg in 1953 was elected director of Radiumhemmet Sven Hultberg took up his post at a time when great changes were taking place in the treatment of malignant tumors and when new methods involving the use of radioisotopes hormones and cytostatics, as well as high energy radiation from cobalt 60 betatrons and linear accelerators were being introduced Under Hultberg's energetic and far seeing leadership these new methods were also introduced at Radiumhemmet and new sections were opened at the hospital It was soon found that cobalt 60 was superior to radium in many respects and as Hultberg did not consider the cobalt apparatus then in use to meet his requirements for adequate radiation the gammatron was designed and constructed as a result of collaboration between Hultberg and a German firm The experiences gained with this new unit and the measurement results obtained during its development were

described by Hultberg and his co workers at the International Congress of Radiology at Munich in 1958 The equipment at Radiumhemmet was also supplemented with a kilocurie cobalt unit and a 18 MeV betatron

During the last few years of his life Hultberg *was working on a project to* acquire a high voltage station and a new radiobiology department which were to be housed in an annex to Radiumhemmet, but he did not live to see the new departments from which he expected so much The new hematologic and cytologic laboratories at Radiumhemmet were largely a result of Sven Hultberg s interest in cytostatic drug treatment and in the increasing importance attached to cytologic diagnosis

Sven Hultberg was an excellent teacher and lecturer The large textbook on radiation therapy and cancer disease for the Scandinavian countries, published in 1963, was in a large measure the result of his efforts Hultberg was above all a clinician, however His own experience of illness and its effects on the personality may have helped him to a deeper understanding of his patients difficulties and contributed to their great confidence in him

Sven Hultberg was engaged in much organisatory work connected with his profession He was chairman of the Swedish Society of Medical Radiology from 1962—1964 He was the initiator of the Nordic Radiotherapy Society, and its chairman from 1954 to 1964 From 1954 until his death he was Associate Editor and a Member of the Editorial Board of Acta Radiologica His work in the special field he represented and his interest in the activities of the journal were enthusiastic and greatly stimulating His opinions on manuscripts offered for publication were always valuable and greatly appreciated both by the authors themselves and by the journal Sven Hultberg will be sadly missed by the Editorial Board of Acta Radiologica

The Editor

FROM THE DEPARTMENTS OF PHYSIOLOGY, RADIOLOGY AND MEDICINE, UNIVERSITY OF ARKANSAS MEDICAL CENTER AND V. A. SOUTHERN RESEARCH SUPPORT CENTER, LITTLE ROCK, ARKANSAS, U.S.A.

INFLUENCE OF ROENTGEN AND ^{60}CO GAMMA RAYS ON DNA SYNTHESIS IN HAMSTER ORGANS

by

W. LOHMANN, W. F. DENNY, W. H. PERKINS, A. J. MOSS JR. and C. F. FOWLER

The inhibiting effect of ^{60}Co gamma and roentgen irradiations on in vivo synthesis of desoxyribonucleic acid has been reported in a number of systems (KELLY 1957, RICHMOND et coll. 1957, LAJTHA 1960). In most of these experiments the incorporation of ^{32}P into DNA of resting or regenerating liver was studied. It was found that radiation significantly depressed the DNA synthesis. Several workers (OKADA et coll. 1959, BOLLUM et coll. 1960) pointed out that these results might be due to a depression of synthetic enzymes by radiation. VAN LANCKER (1960), however, interpreted his findings as the result of either a direct radiation effect on the DNA macromolecule itself or as an indirect effect on the mechanism which makes DNA available as a primer.

Recently LEHNERT et coll. (1962) found in in vitro experiments using the incorporation of ^{3}H-thymidine into DNA of nuclei isolated from resting livers of rats irradiated with 800 R that DNA synthesis was not significantly inhibited after irradiation. In another in vitro experiment determining the DNA synthesis of human bone marrow cells by the 2 to 4 hour uptake of ^{14}C-thymidine (BERRY et coll. 1961) a similar result was found. After irradiation with 800 R roentgen rays the inhibition of the DNA synthesis was only about 24 %. Since the results obtained in the in vitro experiments might be different for several reasons from in vivo experiments, we have studied the incorporation of ^{14}C-thymidine into DNA in an in vivo experiment.

This work was supported by Publ. Health Service Res. Grant RH 00197, Div. Radiological Health. Submitted for publication 15 February 1965.

In the experiments discussed here, we have investigated the effect of ^{60}Co gamma and roentgen ray irradiations on the in vivo DNA-synthesis in liver kidney, and spleen of hamsters

Materials and Methods For our experiments, 3 month old male Golden Syrian hamsters with an average weight of 105 ± 10 g were used One group was irradiated with ^{60}Co-γ-rays (189 R/min) and a second group with 150 kV roentgenrays (12 mA, 1 mm Al filter, HVL = 4 0 mm Al, 800 R/min) The animals each received a dose of 800 R total body irradiation to the dorsal surface of the body while held in a lucite container

Thirty minutes after irradiation each animal was injected intraperitoneally with 1 μCi ^{14}C thymidine (New England Nuclear Corporation, Boston, Mass) in 0 5 ml sterile isotonic saline

Three groups of five hamsters each were studied (1) control plus ^{14}C thymidine, (2) roentgen treated plus ^{14}C thymidine and (3) ^{60}Co gamma ray-treated plus ^{14}C-thymidine Each experiment was repeated four times and the results expressed as mean values The animals were sacrificed by exsanguination under ether anesthesia 24 hours after irradiation The organs (liver, kidney, and spleen) were placed in 10% TCA at 0° C overnight After drying in an oven at 85° C for 48 hours, the organs were homogenized A portion of each homogenized organ was placed in a stainless steel planchet and assayed for ^{14}C in a gas flow counter (Nuclear Chicago) using methane gas Since small and constant amounts of tissue residue were used for the DNA determination, and the geometrical conditions were kept constant, no corrections for self absorption were necessary

The results obtained by this procedure agreed within error limitations with those obtained by using purified DNA To obtain enough DNA for satisfactory purification, organs from all animals of one group investigated were used for the purification procedure Immediately after sacrificing, the animals' organs were quickly excised, dissected free of extraneous material, and immediately put into Dewar flasks containing liquid nitrogen and stored overnight The SCHMIDT-THANNHAUSER method (1945) was used for the isolation of DNA

Results and Discussion

The specific activities of the DNA (counts per gram organ weight, the term 'DNA' served to signify total cell mass) of irradiated and unirradiated animals are summarized in the Table It may be seen from this data that the spleen of the control animals incorporates considerably more ^{14}C-thymidine than the liver or the kidney This is not surprising since it is known that the formation rate of new cells in normal adult spleen is about 10% (STOHLMAN 1959) com-

Table

Incorporation of C thymidine into DNA of different hamster organs irradiated with 800 R of Co γ or roentgen rays

Organs	Control cpm/g	Co cpm/g	Per cent of unirradiated controls	Roentgen rays cpm/g	Per cent of unirradiated controls
Kidney	140 ± 17	83 ± 11	59	91 ± 14	65
Spleen	2392 ± 359	311 ± 33	13	478 ± 59	20
Liver	107 ± 15	75 ± 10	70	87 ± 11	81

pared to 0 5 to 1 0 % in liver (KELLY 1957) After irradiation, however, the greatest per cent inhibition occurred in the spleen In the liver the incorporation was not significantly depressed Furthermore it can be seen from the Table that there is no significant difference in the value of the organs irradiated with roentgen rays or ^{60}Co gamma rays

The lack of depressive effect on liver is in agreement with the findings of LEHNERT et coll (1962) They found that the incorporation of ^{3}H thymidine into liver nuclei of irradiated rats isolated 24 hours after irradiation with 800 R roentgen was 80 ± 8 % KELLY et coll (1955) and RICHMOND et coll (1957) observed, however a considerable reduction in the two hour ^{32}P incorporation into DNA of resting liver 24 hours after total body irradiation of mice with 800 R roentgen rays The value they found was about 30 % and was felt to be dose independent

Since both experiments were done in vivo the factors resulting in these differences are numerous Species variation probably has an influence since different animals were used There are also obvious differences in the method used by KELLY (1957) and by us Thymidine is utilized only in DNA synthesis during the interphase (S phase) Because the reduction of ^{14}C thymidine incorporation into the liver DNA after irradiation is negligible it might be concluded that irradiation during the S phase does not have a significant influence on ^{14}C-thymidine incorporation

In contrast to the results obtained with the incorporation of thymidine in the liver are the results obtained with the kidney and spleen In these organs there obviously was a radiation influence in the nuclei during the S phase which resulted in an inhibition of DNA synthesis

Acknowledgements

The assistance of Mrs Luanne Hicklin and Mr Harry Thompson is greatfully acknowledged

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Thirty minutes after irradiation each animal was injected intraperitoneally with 1 μCi ^{14}C thymidine (New England Nuclear Corporation, Boston, Mass) in 0 5 ml sterile isotonic saline

Three groups of five hamsters each were studied (1) control plus ^{14}C thymidine, (2) roentgen treated plus ^{14}C-thymidine and (3) ^{60}Co gamma ray treated plus ^{14}C thymidine Each experiment was repeated four times and the results expressed as mean values The animals were sacrificed by exsanguination under ether anesthesia 24 hours after irradiation The organs (liver, kidney, and spleen) were placed in 10% TCA at 0° C overnight After drying in an oven at 85° C for 48 hours, the organs were homogenized A portion of each homogenized organ was placed in a stainless steel planchet and assayed for ^{14}C in a gas flow counter (Nuclear-Chicago) using methane gas Since small and constant amounts of tissue residue were used for the DNA determination, and the geometrical conditions were kept constant, no corrections for self absorption were necessary

The results obtained by this procedure agreed within error limitations with those obtained by using purified DNA To obtain enough DNA for satisfactory purification, organs from all animals of one group investigated were used for the purification procedure Immediately after sacrificing the animals' organs were quickly excised, dissected free of extraneous material, and immediately put into Dewar flasks containing liquid nitrogen and stored overnight The SCHMIDT-THANNHAUSER method (1945) was used for the isolation of DNA

Results and Discussion

The specific activities of the DNA (counts per gram organ weight, the term 'DNA' served to signify total cell mass) of irradiated and unirradiated animals are summarized in the Table It may be seen from this data that the spleen of the control animals incorporates considerably more ^{14}C thymidine than the liver or the kidney This is not surprising since it is known that the formation rate of new cells in normal adult spleen is about 10% (STOHLMAN 1959) com

Table

Incorporation of C[14] thymidine into DNA of different hamster organs irradiated with 800 R of Co-γ or roentgen rays

Organs	Control cpm/g	Co cpm/g	Per cent of unirradiated controls	Roentgen rays cpm/g	Per cent of unirradiated controls
Kidney	140 ± 17	83 ± 11	59	91 ± 14	65
Spleen	239 ± 359	311 ± 33	13	478 ± 59	20
Liver	107 ± 15	75 ± 10	70	87 ± 11	81

pared to 0 5 to 1 0 % in liver (KELLY 1957) After irradiation, however, the greatest per cent inhibition occurred in the spleen In the liver the incorpora tion was not significantly depressed Furthermore, it can be seen from the Table that there is no significant difference in the values of the organs irra diated with roentgen rays or ^{60}Co gamma rays

The lack of depressive effect on liver is in agreement with the findings of LEHNERT et coll (1962) They found that the incorporation of ^{3}H thymidine into liver nuclei of irradiated rats isolated 24 hours after irradiation with 800 R roentgen was 80 ± 8 % KELLY et coll (1955) and RICHMOND et coll (1957) observed, however a considerable reduction in the two hour ^{32}P incorporation into DNA of resting liver 24 hours after total body irradiation of mice with 800 R roentgen rays The value they found was about 30 % and was felt to be dose independent

Since both experiments were done in vivo the factors resulting in these differences are numerous Species variation probably has an influence since different animals were used There are also obvious differences in the method used by KELLY (1957) and by us Thymidine is utilized only in DNA synthesis during the interphase (S phase) Because the reduction of ^{14}C-thymidine incorporation into the liver DNA after irradiation is negligible, it might be concluded that irradiation during the S phase does not have a significant influence on ^{14}C-thymidine incorporation

In contrast to the results obtained with the incorporation of thymidine in the liver are the results obtained with the kidney and spleen In these organs there obviously was a radiation influence in the nuclei during the S-phase which resulted in an inhibition of DNA synthesis

Acknowledgements

The assistance of Mrs Luanne Hicklin and Mr Harry Thompson is greatfully acknowledged

SUMMARY

The incorporation of ^{14}C thymidine into DNA in kidney, liver, and spleen of hamsters after whole body roentgen or ^{60}Co gamma irradiation with 800 R was investigated The DNA activity was determined 24 hours after irradiation Compared to the control values the values for the roentgen irradiated and gamma irradiated animals were liver 81 % (70 %) kidney 65 % (59 %) and spleen 20 % (13 %) The data are discussed in relation to radiation damage at the cellular level

ZUSAMMENFASSUNG

Es wurde die Aufnahme von ^{14}C Thymidin in DNS der Niere der Leber und der Milz von Hamstern nach Ganzkorper Rontgenbestrahlung oder ^{60}Co γ Bestrahlung mit 800 R untersucht Es wurde die DNS Aktivität 24 Stunden nach der Bestrahlung bestimmt Verglichen mit den Kontrollwerten sind die Werte der mit Röntgen und mit Gamma bestrahlten Tiere Leber 81 % (70 %), Niere 65 % (59 %) und Milz 20 % (13 %) Diese Ergebnisse werden in Bezug auf die Strahlungsschaden der Zelle besprochen

RÉSUMÉ

Les auteurs ont étudié l incorporation de thymidine ^{14}C dans l ADN du rein du foie et de la rate de hamsters après irradiation de tout le corps par 800 R de rayons roentgen ou de rayons gamma du ^{60}Co L activité de l ADN a été mesurée 24 heures après l irradiation Comparée à l activité des animaux témoins celle des animaux irradiés par les rayons de roentgen et par les rayons gamma sont foie 81 % (70 %) rein 65 % (59) et rate 20 % (13 %) Ces résultats sont examinés en fonction des radiolésions au niveau cellulaire

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FROM THE DIVISION OF RADIOBIOLOGY (DIRECTOR DOCENT ARNE NELSON),
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EARLY DEVELOPMENT OF TRANSPLANTED ^{90}Sr INDUCED OSTEOSARCOMA BUDS

by

AGNAR NILSSON

Strontium 90 induced osteosarcoma arises in foci of cell proliferation (buds) in endosteal tissue or *reticulum cells in the* marrow cavity Buds develop multicentrically in one or several bones at the same time, and even in their intramedullary phase of development they have acquired autonomy (NILSSON 1962b) Buds dissected out at an *early stage*, 150 to 180 *days* after the administration of ^{90}Sr can be transplanted *in isologous mice* After a period ranging from a few weeks to a few months the transplanted buds display the characteristics of a *malignant* tumour with massive metastases (NILSSON & ULLBERG 1962) *The microscopic* appearances of the original bud and the transplants are very similar

The purpose of the present studies has been to ascertain whether intramedullary osteosarcoma buds that arise late like those occurring earlier are capable of developing into malignant tumours when removed from the influence of ^{90}Sr Tumour buds found 294 to 378 days after the administration of ^{90}Sr have been *utilized for the* experiments A more detailed study *of the*

Submitted for publication 25 March 1965



Fig 1 Roentgenogram of normal mouse × 2

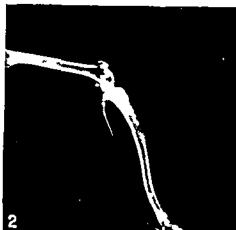


Fig 2 Roentgenogram (T 23) at 343 days after ^{90}Sr treatment Mineralized tumour bud in proximal part of left tibia × 2

early fate of such transplants has also been performed to determine the morphologic criteria of malignancy and the surrounding tissue reaction

The tumour buds have been examined histologically at intervals, the earliest time being six days after implantation

Material and Methods Male CBA mice from brother sister matings in the strain kept at our laboratory were used The animals were fed a standard diet ad libitum and kept under standard conditions Thirty mice without macroscopically visible tumours were taken at random from a group of animals that had been injected i p 294 days previously with 0 9 μCi $^{90}Sr(NO_3)$ per gram bodyweight The thirty mice were radiographed and three were found ot have evidence or signs of osteosarcoma buds The procedure was repeated for the remaining mice 315 (two buds detected), 343 (two buds) and 378 (one bud) days after the injection of ^{90}Sr

The mice were anaesthetized with 0 15 to 0 30 ml mebumal 0 6 % for radiography and then killed by dislocation of the neck

The size of mouse bones limited the study to buds in the femur and tibia The buds were dissected aseptically, and dehydration during the time consuming process was avoided by flooding with sterile 0 9 per cent NaCl solution Care was taken to remove as much pre formed bone as possible from the buds so that development after transplantation would be in an environment with a minimum of ^{90}Sr (NILSSON & ULLBERG 1962b) As soon as the buds were dissected free they were transplanted subcutaneously into ^{90}Sr free, isologous



Fig 3 Section of the tumour bud shown in fig 2 Necrosis of epiphyseal cartilage and prominent production of immature bone van Gieson × 100



Fig 4 Transplant of tissue from the bud in figs 2 and 3 at 128 days the transplant had attained a diameter of 2 cm (cf histologic appearances of parent tissue and transplant) van Gieson × 100

male CBA mice through a 0 5 cm incision in the dorsal aspect of the neck, the incision was closed with clips and sprayed with Nobecutan plastic film

A small piece of the bud was fixed in Stieve s fluid embedded in paraffin and stained by van Gieson s method for comparison of histologic type at the time of transplantation and later

Subsequent development of the tumour was followed by palpation Mice,

Table

Mouse number	Transplantation of intramedullary tumour buds				
	Appearence of tumour buds days	Site	Histologic type		Takes in days
			Original bud	Transplants	
T 3	294	L Femur	Osteoblastic	Predom osteoblastic	52
T 25A	294	R Femur	»	Osteoblastic	19
T 25B	294	L Femur	»	»	19—130
T 7	315	R Femur	»	»	34
T 11	315	R Femur	»	»	173
T 23	343	L Tibia	»	»	12
T 15B	343	R Femur	Fibroblastic	Fibroblastic	12
T 17	378	L Femur	»	»	14



Fig 5 Intramedullary osteoblastic bud from right femur at 342 days after i p injection of ^{90}Sr van Gieson × 40



Fig 6 Tangential section of tissue from bud in fig 5 transplanted 6 days earlier subcutaneously in dorsal neck region of syngenic mouse ten dency to capsule formation and cellular degen eration van Gieson × 40

bearing the transplants, were killed when the tumours reached a diameter of about 2 cm A sample of the tumour was then taken, and fixed and stained, as was the case with the original osteosarcoma buds

An additional series of five transplants was set up in the same manner for study of the local reaction to the transplanted buds Four of the buds were of the osteoblastic type and one of the fibroblastic type The mice bearing the trans plants were killed after 6, 35, 47, 49 and 55 days, and the transplanted buds together with the surrounding subcutaneous tissue and skin were dissected out After paraffin embedding, the tissue block was then sectioned serially Samples of the bud were taken at the time of transplantation for comparison Three mice, bearing transplants of 2 mm long segments of the distal metaphysis of the femur of normal mice, served as controls These mice were killed after intervals of 6, 18 and 27 days

Results

Details of the osteosarcoma buds are listed in the Table, which includes the time the buds were taken, their original site, their histologic type, and the



F g 7 Transplant from osteoblastic bud 35 days fter *transplantat on prol feration of cells nside* the capsule van Gieson × 40



Fig 8 Bud tissue 55 days after transplantation no macroscopical growth clone of cells van G eson × 400

interval between transplantation and the beginning of detectable increase in si e *This interval* differed greatly for the different buds, from 12 to 173 days for *the osteoblastic* osteosarcoma buds and much shorter for the two fibro blastic buds examined The over all mean was 55 8 ± 21 8 days *Once estab* lished the transplanted fibroblastic buds increased in size more rapidly than the osteoblastic buds

As *in* previous series (NILSSON 1962b), the microscopic appearances of the transplants were very similar to that of the original bud *(Figs 3 to 4)*

Local reaction at the site of transplantation was practically limited to the formation of a thin fibrous capsule The reaction both qualitatively and quantitatively was much the same for the normal bone transplants (Figs 13 and 14) as the tumour bud transplants (Figs 6 7 and 11) Capsule formation with lively fibroblast proliferation and the presence of stainable collagen fibres were evident six days after transplantation No lymphocytes were present in the area and only a few granulocytes and macrophages were found In the



Fig 5 Intramedullary osteoblastic bud from right femur at 342 days after i p injection of ^{90}Sr van Gieson × 40



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Results

Details of the osteosarcoma buds are listed in the Table, which includes the time the buds were taken, their original site, their histologic type, and the



Fig 11 Transplant from bud shown in *fig 9* at *49* days after subcutaneous transplantation tendency to capsule formation slight reaction in subcutaneous tissue van Gieson × 40



Fig 12 Enlargement of portion from fig 11 Highly vascularized tissue many pycnotic nuclei and a mitotic figure van Gieson × 400

not evident in the buds that had not begun to grow The microscopical appearances of the original buds and the transplants were similar in this series as well (Figs 9 to 12)

Discussion

It has already been demonstrated that intramedullary osteosarcoma buds arising 150 to 180 days after the administration of ^{90}Sr are not dependent upon the continued influence of ^{90}Sr for development into autonomous malignant tumours with a great propensity for metastasizing (NILSSON 1962b NILSSON & ULLBERG 1962a) The microscopic similarity between the buds and the transplants has been demonstrated in both the previous and the present series It has also been determined that buds transplanted at a longer interval after the administration of ^{90}Sr also have autonomous properties In general then it appears that once the ^{90}Sr induced intramedullary buds arise they are not dependent upon the continued presence of ^{90}Sr in their environment for retention of their potentially malignant properties The ^{90}Sr concentration, even in heavily mineralized buds is so low (NILSSON & ULLBERG 1962b) that it is



Fig 9 Intramedullary fibroblastic bud left femur 342 days after i p injection of ^{90}Sr van Gieson × 40

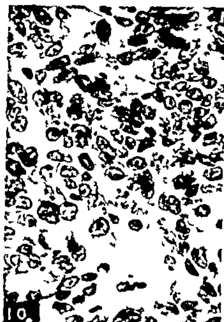


Fig 10 Enlargement of portion of fig 9 van Gieson × 400

early period after transplantation there were no signs of infiltration of tumour cells outside the capsule Later on, 2 1/2 to 4 months after transplantation as revealed in an additional experiment, there was lively infiltration of the adjacent subcutaneous and muscle tissue in spite of the tumour having a marked tendency to grow expansively as well Numerous macrophages, particularly well demonstrated by intravital trypan blue staining, were evident along the border between the tumour and the surrounding tissues

Widespread degeneration of osteocytes and bone marrow cells was apparent in the transplants, tumour bud, or normal bone six days after transplantation (Figs 6 and 13) Most lacunae contained pyknotic osteocytes Numerous empty lacunae as well as intact osteocytes were evident in later samples of the bone and bud transplants (Fig 15) Eighteen days after transplantation, the marrow *of the normal bone was still hypoplastic but regeneration centres had appeared* There were no signs of osteoclastosis or foreign body reaction

Two bud transplants were examined before and three after detectable growth had begun Few cells lay between the trabeculae in the buds before growth commenced but in many places there were groups of large light cells that appeared to be intact (Fig 8) A well developed capillary network was present in the three bud transplants examined after growth had commenced but was



Fig 11 Transplant from bud shown in fig 9 at 49 days after subcutaneous transplantation tendency to capsule formation slight reaction in subcutaneous tissue van Gieson × 40

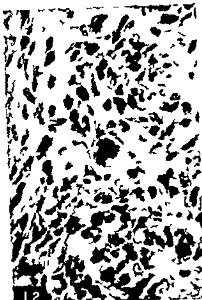


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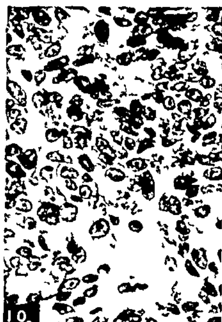


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Fig 15 Normal femur 18 days after transplantation Empty lacunae in compact bone and formation of capsule van Gieson × 250

transplants of this type begin to grow sooner than transplants of the osteoblastic type

The slight reaction of the recipient tissues to the presence of the transplant can be explained by the donors and recipients being syngenous and the weak antigenic capacity of the tumour (RÉVÉSZ NILSSON & STJERNSWARD not yet published) Normal bone tissue from CBA mice transplanted into C_3H mice induces a strong reaction at the site Skin transplants between males of the CBA strain used for these studies have been retained during observation periods of 30 days

There are no differences between transplants of tumour buds and normal bone in the rapidity with which the transplant is enclosed in a fibrous capsule or the degree of fibroblast activity in the surroundings The gathering of macrophages along the border between the transplanted tumour and its surroundings is likely the result of local tissue destruction through expansion or infiltration of the tumour

The early degenerative changes in the osteocytes and marrow cells are temporary and probably represent an initially inadequate vascular supply since no signs of necrosis and lysis of the transplanted tissue were evident later on

In the transplanted buds that were examined before growth had commenced there were small groups of polymorphic cells which very likely are clones of intact tumour cells which when adequate vascularization is established, are the source of further growth of the tumour The anoxia immediately after transplantation leads to a selection of the more resistant tumour cells possibly part of the explanation why the growth of serially transplanted tumours begins earlier and is more rapid in successive generations (NILSSON unpublished)

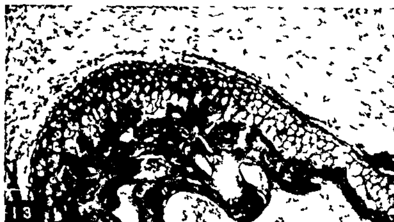


Fig 13 Normal femur subcutaneously transplanted 6 days earlier formation of capsule pycnotic bone marrow cells and osteocytes van Gieson × 100

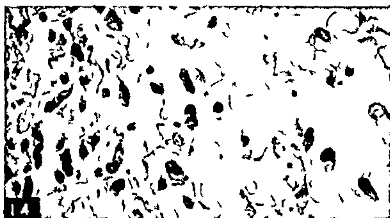


Fig 14 Increased fibroblastic activity in subcutaneous tissue outside the capsule in fig 13 Formation of fibres two granulocytes present van Gieson × 400

unlikely to have any effect upon further development of the buds after transplantation The mice from which the buds were obtained did not have any macroscopically visible tumours, this eliminates the possibility of the buds taken for transplantation being metastases

The predominantly fibroblastic, weakly bone forming osteosarcomas represent a lower degree of differentiation than the osteoblastic tumours (NILSSON 1962a, WILTON 1962) and the fibroblastic buds grow more rapidly than the osteoblastic The acquisition of an efficient vascular supply is also associated with more rapid growth The more rapid development of a capillary network in the poorly bone forming tumours may be part of the reason why

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EFFECT OF BREATHING 5 % CARBON DIOXIDE AND 95 % OXYGEN AT ATMOSPHERIC PRESSURE ON TUMOUR RADIOCURABILITY

by

W R INCH J A McCREDIE and J KRUUV

The amount of cellular damage produced by ionizing radiation depends largely upon the concentration of oxygen in the tissues at the time of their exposure The ratio of aerobic to anaerobic sensitivity is a function of the linear energy transfer (LET) of the radiation it is about three for low LET radiations such as roentgen and gamma rays nearly two for neutrons and only slightly greater than one for alfa particles which have a high LET (6) Malignant tumours unlike normal tissues have a poorly developed blood supply and contain cells which vary in their oxygenation and nutrition They can be considered to contain cords of well oxygenated radiosensitive cells adjacent to blood vessels areas where the cells maintain their reproductive integrity largely by anaerobic glycolysis and are radioresistant and foci of necrosis Although the radioresistant cells may represent only a small fraction of the

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SUMMARY

The development of ^{90}Sr induced intramedullary osteosarcoma buds has been studied after transplantation to syngenous mice. The buds are autonomous and not dependent upon the continued presence of ^{90}Sr in their environment in order to maintain their potentially malignant properties and develop into osteosarcoma.

ZUSAMMENFASSUNG

Die Entwicklung von intramedullaren Osteosarkomkeimen, die durch ^{90}Sr hervorgerufen waren, wurde an gleichrassigen Mausen nach deren Transplantation untersucht. Die Keime sind autonom und hängen nicht von der Gegenwart des ^{90}Sr ab betreffend ihrer potentiell malignen Eigenschaften und einer Entwicklung in ein Osteosarkom.

RÉSUMÉ

Le développement de bourgeons d'ostéosarcome intramédullaire induit par ^{90}Sr a été étudié par transplantation sur des souris de même souche. Ces bourgeons sont autonomes et n'ont pas besoin de la présence continue de ^{90}Sr dans leur voisinage pour garder leurs propriétés potentiellement malignes et pour se développer en ostéosarcome.

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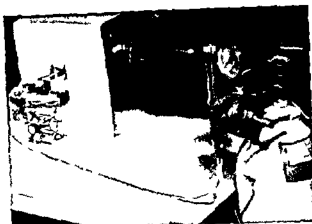


Fig 2 C3H mouse fitted with head mask and immobilized on jig ready for tumour irradiation

fore performed to find the effect of breathing at one atmosphere 5 % CO_2 and 95 % O_2 100 % O_2 or air on the radiocurability of two isologous *murine* transplants, tumours were grown subcutaneously on the back and treated by a microradiotherapy technique to minimize the amount of radiation given to vital tissues The effect of the gases on heart rate respiration and tumour blood flow was also studied

Methods

A piece of the spontaneous mammary carcinoma occurring in the C3H strain of mice or the C3HBA (obtained from Roscoe B Jackson Memorial Laboratory Bar Harbor Maine) tumour was injected aseptically by trocar into the dorsal subcutaneous tissues of 10 to 12 weeks old female C3H/HeJ (obtained from Roscoe B Jackson Memorial Laboratory Bar Harbor Maine) off spring the implant weighed 6 ± 2 mg and contained about 3×10^4 viable cells The C3H isoimplant *is a nodular* tumour containing carcinoma cells arranged in acini and sheets it becomes cystic and develops areas of necrosis in the centre of the nodules at a diameter of *about 0 5 cm There* is a fibrous capsule which is penetrated by a number of blood vessels mainly at the base and occasionally by processes of cancer cells The C3HBA isotransplant is more cellular, has a better blood supply and grows more rapidly (Fig 1) Both tumours are immunologically compatible *with their hosts* and simulate closely the conditions in humans

A number of physiologic factors were studied in the animals while breathing the gases Respiration was measured *using an* electromagnetic pick up

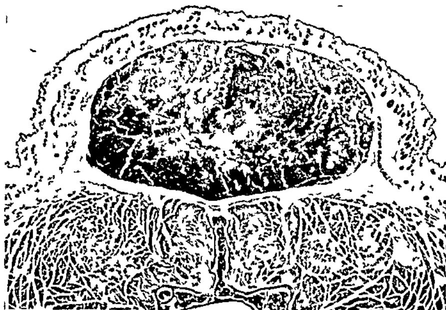


Fig. 1. C3HBA isotransplant (0.032 cm³) 8 days after implantation showing cysts and lack of homogeneity. H. and E. × 20.

tumour, they are often responsible for the failure of radiotherapy to produce a cure (13). Attempts have been made to improve oxygenation during treatment by the local and intra-arterial injection of hydrogen peroxide (14) or oxygen (16) and by inhalation of oxygen at one to four atmospheres (3, 10, 15); however, if the blood flow is poor these adjunctive treatments are of little benefit. The results of using vasodilator and vasopressor drugs have also been disappointing (2).

The addition of a small amount of carbon dioxide to the gas breathed by an animal causes hyperventilation, an increase in blood pressure, dilation of capillaries and gaseous exchange across the endothelial wall. HOLLCROFT *et coll.* (*1951*) gave *1 300* rad roentgen radiation to a transplanted murine lymphosarcoma while the animals breathed at atmospheric pressure 5 % carbon dioxide (CO_2) and 95 % oxygen (O_2), 8 % O_2 and 92 % nitrogen or air; they found the effect on tumour growth was maximal four days after treatment and was greatest in animals given carbon dioxide and oxygen. DU SAULT (1963, 1964) compared the curability of the spontaneous mammary carcinoma in C3H mice breathing 5 % CO_2 and 95 % O_2 at atmospheric pressure with 100 % O_2 at three atmospheres. The mixture of gases produced almost the same increase in rate of cure as hyperbaric oxygen; however, a large dose of roentgen radiation was used and many animals developed severe systemic reaction which could have influenced the results. An experiment was there-

Table

Effect of breathin 5 % and 95 % CO_2 at atmospheric pressure during irradiation on cure of murine tumours

Gas b eathed during irradiat on (4 000 rad)	C3H Isoimplant		C3HBA Isotransplant	
	Number of mice	Fract on cured ( )	Number of mice	Fraction cured ( )
Air	49	25	55	20
100 O	47	38 (P<0 05)	52	38 (P<0 05)
5 CO + 95 O	51	55 P<0 01)	53	40 (P<0 05)

parallel opposed fields Animals were killed and autopsied when the tumour recurred and survivors at 100 days were considered cured

Results

The animals were anaesthetized 30 min before starting the physiologic measurements, they were maintained on each gas for a period of 20 min since this corresponded to the time during which irradiation was given Inhalation of 100 % O_2 did not alter tumour blood flow or heart rate (Fig 3) it increased rectal temperature by 0 3 C and decreased the rate (9 %) and depth of respiration Breathing the mixture of gases increased tumour blood flow by about 30 % and respiration rate by 4 % but decreased heart rate (8 %) and rectal temperature (1 0 C) The changes were maximal 3 to 5 min after giving the gas and the effects began to decrease after about 15 min The cure rate of both tumours was increased in animals irradiated while breathing 5 % CO_2 and 95 % O_2 compared with those given air (see Table) however the cure rate of the C3H isoimplant but not of the C3HBA isotrans plant was significantly greater in animals breathing the mixture compared with oxygen None of the animals became ill or died from the effects of the treatment a number from each group were killed four days after the last irradiation and microscopic sections of the tumours were prepared Damage was greatest in tumour irradiated while the animals inhaled the gas mixture which was consistent with the increase in cure rate The C3HBA isotransplant was almost completely destroyed the only remaining malignant tissue was situated toward the superficial surface of the growth in an area where the blood supply was poor (Figs 4 and 5)

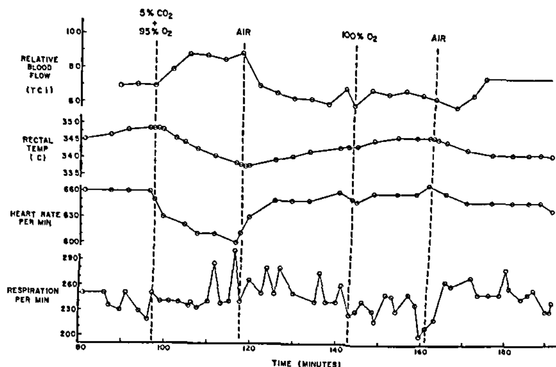


Fig. 3. Variation in physiological parameters in the C3H mouse breathing different gases at atmospheric pressure.

touching the chest, integrated electronically and the rate was recorded on a fast time response strip chart recorder. An electrocardiograph with leads attached to the chest, back and leg was used to determine the heart rate. The temperatures in the rectum (T_r), on the skin overlying the tumour (T_t) and in the surrounding air (T_a) were monitored by means of bead thermistors and the thermal circulation index [T.C.I. = $(T_t - T_r) / (T_r - T_a)$] which is proportional to blood flow in the tumour was calculated. Animals were anaesthetized for these measurements by a single intraperitoneal injection of urethane (1.75 g/kg); this was effective for up to three hours and caused only a slight increase in heart rate while barbiturates depressed all parameters.

When the maximal dimension of the growth was 0.8 ± 0.2 cm the animals were divided into three groups. They were immobilized for irradiation without anaesthetic on a special treatment jig and fitted with a plastic head mask which was connected to 5 % CO_2 and 95 % O_2, 100 % O_2 or air (Fig. 2); they breathed the gas for five minutes before and during treatment. Radiation was given using a 200 kV Picker X-ray unit, fitted with a 1.5 × 2.0 cm cone focal skin distance of 25 cm and output of 375 rad/min; the dose (4000 rad) was divided into two fractions separated by four days and given through

Table

Effect of breathing 5 % and 95 % CO_2 at atmospheric pressure during irradiation on cure of murine tumours

Gas breathed during radiation (4 000 rad)	C3H Isoimplant		C3HBA Isotransplant	
	Number of mice	Fraction cured (%)	Number of mice	Fraction cured (%)
Air	49	25	55	20
100 % O_2	47	38 ($P<0.05$)	52	38 ($P<0.05$)
5 % CO_2 + 95 % O_2	51	55 ($P<0.01$)	53	40 ($P<0.05$)

parallel opposed fields Animals were killed and autopsied when the tumour recurred and survivors at 100 days were considered cured

Results

The animals were anaesthetized 30 min before starting the physiologic measurements they were maintained on each gas for a period of 20 min since this corresponded to the time during which irradiation was given Inhalation of 100 % O_2 did not alter tumour blood flow or heart rate (Fig 3) it increased rectal temperature by 0 3 C and decreased the rate (9 %) and depth of respiration Breathing the mixture of gases increased tumour blood flow by about 30 % and respiration rate by 4 % but decreased heart rate (8 %) and rectal temperature (1 0 C) The changes were maximal 3 to 5 min after giving the gas and the effects began to decrease after about 15 min The cure rate of both tumours was increased in animals irradiated while breathing 5 % CO_2 and 95 % O compared with those given air (see Table) however the cure rate of the C3H isoimplant, but not of the C3HBA isotransplant was significantly greater in animals breathing the mixture compared with oxygen None of the animals became ill or died from the effects of the treatment a number from each group were killed four days after the last irradiation and microscopic sections of the tumours were prepared Damage was greatest in tumour irradiated while the animals inhaled the gas mixture which was consistent with the increase in cure rate The C3HBA isotransplant was almost completely destroyed the only remaining malignant tissue was situated toward the superficial surface of the growth in an area where the blood supply was poor (Figs 4 and 5)

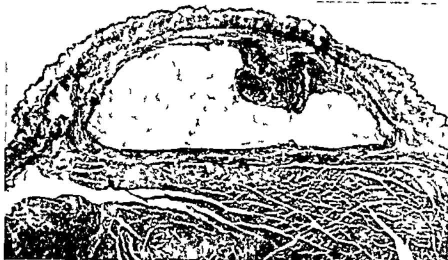


Fig. 4. C3HBA isotransplant 4 days after second irradiation: malignant tissue destroyed except for small area toward superficial surface. H. and E. × 20



Fig. 5. Remaining malignant tissue showing extensive damage, lack of mitoses and haemorrhagic areas. H. and E. × 220

Discussion

The results showed that *inhalation of 5 % carbon dioxide and 95 % oxygen* at atmospheric pressure increased the radiocurability of the C3H isoimplant. The carbon dioxide increased blood flow to the many anoxic areas in the tumour by raising the systemic blood pressure and dilating and increasing permeability of the capillaries. Blood oxygen tension and the amount of oxygen

carried in solution in the plasma increased markedly although there was little increase in that transported by haemoglobin, oxygenation was therefore improved and radiosensitivity increased

Pure oxygen at atmospheric pressure did not affect the blood flow and has been reported to produce a decrease in normal tissues (1) An increase in systemic blood oxygen tension would therefore not be of as much benefit to areas in a tumour that already had a good blood supply

The gas mixture that provides maximal tissue oxygenation without producing severe side effects has not been determined Five per cent carbon dioxide in air has been breathed by patients with cerebro vascular disease for 10 minutes without serious discomfort and this is probably the highest concentration that can be used clinically (8) the best mixture may therefore contain 5 % carbon dioxide and oxygen diluted with nitrogen A hyperbaric mixture may further increase the radiocurability of some tumours however its composition would likely be different

Cure of the C3HBA isotransplant was not increased by adding CO to the gas breathed compared with 100 % O_2 probably because its blood supply was better it was more uniformly oxygenated and was less necrotic In preliminary experiments we have found that the vasodilator drug nitroglycerin increased tumour blood flow almost as much as inhalation of the gas mixture and would therefore be expected to increase the rate of cure of the tumours by radiation However since the concentration of carbon dioxide is easily varied and the effect is controlable inhalation of the gas would appear to be the method of choice Use of a platinum microelectrode (11) to measure oxygen diffusion current in the tumour when a patient inhales a gas mixture, is given a drug or is pressurized in pure oxygen may help to assess the best form of treatment

Implanted and transplanted isologous tumours were used in this study rather than spontaneous growths to minimize the integral dose and avoid irradiating vital tissues MARGULIS et coll (1961) have shown that the blood supply of the transplanted C3H tumour is the same as that of the spontaneous growth blood vessels are sparse and the major ones originate from the tumour base A similar blood supply is seen in patients with cancer of the colon (7) however other tumours such as renal metastases and osteogenic sarcoma generally have a rich blood supply

Conclusions

The effect of breathing 5 % carbon dioxide and 95 % oxygen at atmospheric pressure on blood flow body temperature and respiration was determined in the C3H mouse blood flow and respiratory rate were increased

and body temperature and heart rate decreased compared with animals breathing air Pure oxygen at atmospheric pressure did not affect blood flow or heart rate, decreased respiration and increased body temperature Inhalation of the mixture of gases during irradiation increased the cure of the C3H isoimplant, which contained many necrotic foci, compared with animals given pure oxygen or air The rate of cure of the well vascularized C3HBA isotransplant was increased by the mixture compared with air but not with pure oxygen

Acknowledgements

The authors are indebted to Mistresses R Stodolski M Alderson L Melnick and Y Fotheringham who carried out the irradiations and collected and analysed the data and to Mr D Pulham who took the photographs

SUMMARY

Inhalation of 5 % carbon dioxide and 95 % oxygen at atmospheric pressure increased blood flow and radiocurability of the poorly vascularized C3H isoimplant in the mouse compared with breathing 100 % oxygen The rate of cure of the C3HBA isotransplant which has a better blood supply was increased compared with air but not with pure oxygen

ZUSAMMENFASSUNG

Die Einatmung von 5 % Kohlendioxyd und 95 % Sauerstoff bei atmospharischem Druck erhohte die Blutzirkulation und die Heilung durch Rontgenstrahlen eines sparlich durchbluteten C3H Isoimplantates an der Maus verglichen mit einer Atmung mit 100 % Sauerstoff Hingegen war der Grad der Heilung des C3HBA Isotransplantates das eine bessere Blutversorgung hat erhoht verglichen mit Luft jedoch nicht erhoht verglichen mit reinem Sauerstoff

RÉSUMÉ

Par rapport a l inhalation d oxygene pur l inhalation de 5 % de gaz carbonique et de 95 % d oxygene a la pression atmosphérique augmente le débit sanguin et la radiocurabilité de l iso implant C3H mal vascularisé de la souris Le taux de guérison de l isotransplant C3HBA qui est mieux vascularisé a été augmenté par rapport a l air mais non par rapport à l oxygène pur

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Par rapport a l inhalation d oxygène pur l inhalation de 5 % de gaz carbonique et de 95 % d oxygène à la pression atmosphérique augmente le débit sanguin et la radiocurabilité de l iso implant C3H mal vascularisé de la souris Le taux de guérison de l isotransplant C3HBA qui est mieux vascularisé a été augmenté par rapport a l air mais non par rapport à l oxygène pur

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COMPARED EFFECTS OF RADIOSTRONTIUM AND ROENTGEN RAYS ON GERM CELLS IN MALE MICE

by

B. HENRICSON and A. NILSSON

The effect of ^{90}Sr on male gonads has been studied by several workers. TRUSOVA (1956) reported periodic disturbances of the sperm activity on long term dietary administration of ^{90}Sr in dogs with a decrease in volume of the ejaculate and an increased frequency of atypical forms of spermatozoa; the ejaculates were radioactive. These results were confirmed by BURYKINA & TRUSOVA (1963) in a series of dogs given ^{90}Sr orally for 24 to 40 months. BURYKINA (1957) described a reduction and change in the spermatogenesis in rats after treatment with ^{90}Sr. OWEN et coll. (1957) also found a very much reduced spermatogenesis in rabbits after administration of ^{90}Sr.

ÅBERG & GILLNER (1964) *in an investigation on the effect of a single dose* of ^{90}Sr in rams demonstrated oligospermia, atypical forms of spermatozoa and a considerable incorporation of ^{90}Sr into the single spermatozoa. HENRICSON et coll. (1962) found in mice that the type B spermatogonium does not seem to be so severely affected as the type A spermatogonium. It has also been

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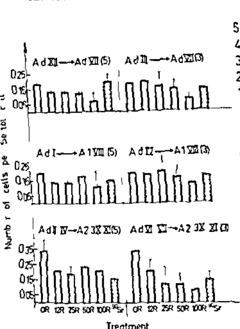


Fig 1 Mean number and 95 confidence limit of spermatogonia type A per Sertoli cell per tubular cross section Symbols to the left of the arrow indicate cell type and tubular stage irradiated, symbols to the right of the arrow indicate those scored
A d — Spermatogonium type A dormant
A 1 — Spermatogonium type A first generation
A —3 — Spermatogonium type A second and third generation
Roman figures indicate tubular stages
Figures (3) and (5) indicate the respective days after treatment see also Table

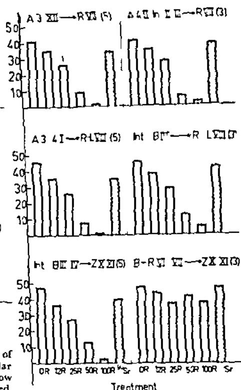


Fig 2 Mean number and 95 confidence limit of primary spermatocytes per Sertoli cell per tubular cross-section Same symbols as in fig 1 (See also Table) Further symbols
Int — Spermatogonia intermediate type
B — Spermatogonia type B
R — Resting primary spermatocytes
L — Leptotene
Z — Zygotene

observed that in embryos from ⁹⁰Sr treated male mice there is a considerable variation in the chromosome numbers (HENRICSON & NILSSON 1964) which may be of interest in connection with the findings by LUNING et coll (1963) of increased intra uterine deaths of embryos with fathers treated with the same dose of ⁹⁰Sr as used by the present authors

As a consequence of these findings there seems to be a great need of more precise information about the ⁹⁰Sr effect on the seminiferous cells The aim of this work was also to evaluate if possible the radiation dose to the testicular tissue from an intravenously injected dose of ⁹⁰Sr by comparing its tissue

destruction effect with that of different doses of roentgen irradiation under standardized conditions As the last mentioned procedure is a total body irradiation, a comparison with the β ray effect of ^{90}Sr on pure physical grounds is very complicated

Material and Methods CBA male mice were used as test animals Fifteen animals were injected intravenously with 0 7 μCi ^{90}Sr per gram bodyweight at the age of 75 days Four groups of 10 mice each received 12, 25, 50 and 100 R of total body roentgen irradiation (Muller MG 300, 260 kV, 10 mA, focal distance 40 cm, inherent filtration 4 mm Al, additional filter 0 5 mm Cu, dose rate 85 R/min) Ten of the strontium treated animals, and 5 from each of the roentgen treated groups, were killed after 72 hours Five strontium treated and the remaining 5 mice in the roentgen treated groups were killed after 120 hours A control group of 10 mice were killed at 75 + 3 days of age The testicles were removed immediately and fixed in Stieves fluid The left testicle was embedded and sectioned at 4 μ and stained according to Hotchkiss' PAS method Ten circular tubular cross sections were selected at random from each of the stages VII, VIII and X XI (OAKBERG 1956) in the cycle of the seminiferous epithelium of the mouse The number of Sertoli cells, spermatogonia type A, resting primary spermatocytes, or those in meiotic prophase (leptotene, zygotene) were counted in the selected tubular cross sections We have chosen to refer the number of germ cells to the number of Sertoli cells in the cross sections even if this procedure is of greater importance at longer intervals between treatment and evaluation (OAKBERG 1959) There is always a variation in tubular diameter but the influence of this when counting a limited number of cross sections can be reduced by reference to the Sertoli cells

Results

The present study covers the effects of ^{90}Sr and roentgen irradiation on several phases in the development from dormant A spermatogonia to intermediate and B spermatogonia The different development phases differ greatly in their sensitivity to irradiation (Figs 1 and 2), apparently a reflection of the critical stages the cells have to pass through in their development (see Table) Cells irradiated in tubule stages XII and III and counted as dormant A-spermatogonia in tubule stage VII after 5 or 3 days (Fig 1, first row) were much less affected than A spermatogonia which had passed through mitosis A reduction in the number of A spermatogonia in stage VII occurred after three days with only 100 R Five days after irradiation there was a depletion also after exposure to 50 R The ^{90}Sr effect was weaker and was apparent only after three days

Table

Cell types and tubular stages involved in the investigation

Irradiation		Stages of cell death	Interval in days between treatment and scoring	Scoring	
Cell type	Stage			Cell type	Stage
A d	XII		3	A d	VII
A d	I		5	AI	VIII
A d	II–III		3	A d	VII
A d	III–IV	VIII X	5	A d + II–III	X–XI
A d	IV	(VIII)	3	AI	VIII
A d	VI–VIII	VIII X	3	A d + II–III	X–XI
AIII	XII	XII II III VI	5	Rest	VII
AIII–IV	I	II III VI	5	Rest Lept	VIII
AIV Int	II–III	III VI	3	Rest	VII
Int B	III–IV	III VI	5	Zyg	X–XI
Int B	IV	VI	3	Rest Lept	VIII
B Rest	VI–VII	VI	3	Zyg	X–XI

In tubule stage VIII the cells which were dormant A spermatogonia in tubule stage I and IV at the time of irradiation were counted as first generation A spermatogonia (Fig 1 second row) The appearance of the tubules varied somewhat and a cell depletion could be traced only for the 100 R group but not for the ^{90}Sr groups

There was a significant cell reduction in the ^{90}Sr groups and most of the roentgen groups for the tubules in stage X XI i e after A spermatogonia had passed through the period of DNA synthesis in stage VIII and X and become A spermatogonia of the second and to some extent of the third generation (Fig 1 third row) The cell reduction for all roentgen groups was higher three days after irradiation than after five days the difference being particularly evident after 50 and 100 R There were no comparable differences between the ^{90}Sr groups

Most mice in all the roentgen groups exhibited a highly significant depletion of cells which at the time of irradiation were third and fourth generation A spermatogonia and five days later were resting cells and leptotene nuclei in stages VII and VIII after having passed through several periods of DNA synthesis (see Table and Fig 2) A statistically significant cell reduction was evident for the ^{90}Sr group only in stage VIII after 5 days

Intermediate and B spermatogonia that three and five days after irradiation were counted as resting leptotene nuclei in stage VIII, and as zygotene nuclei

in stage X—XI, were quite sensitive to roentgen irradiation but were strongly resistant to treatment with ^{90}Sr. Irradiation with 12 R had an effect equal to or exceeding that of the ^{90}Sr dose on these cells (Fig. 2, second and third rows).

Cells that at the time of irradiation were B spermatogonia, or resting cells in stage VI—VII, and three days later were counted as zygotene nuclei in stage X—XI, were highly resistant to irradiation with roentgen rays and not at all affected by ^{90}Sr (Fig. 2, third row).

Discussion

The CBA strain used in the experiments seems to give about the same response to roentgen irradiation as the F_1 hybride of the 101 and the C$_3$H strains used by OAKBERG (1957), although the particular CBA strain employed is possibly somewhat more resistant.

Our results concerning the roentgen doses seem to agree with the findings (OAKBERG 1957, and MONESI 1962) that there is a very marked difference in sensitivity between dormant spermatogonia type A and later stages of the A type plus the intermediate and type B spermatogonia. The LD_{50} of late type A intermediate and type B of 20—24 R roentgen irradiation given by OAKBERG (1957) corresponds to a somewhat higher value here.

The observation that dormant A spermatogonia which have been irradiated in stages III—IV and VI—VII and scored 5 and 3 days later in stage X—XI, also react significantly to 25 R roentgen rays is of great interest. The reason for this sensitivity seems to be that the dormant A is irradiated close to the critical stage of DNA synthesis in stage VIII. This assumption seems to agree with MONESI's (1962) findings that the critical period of cell killing is that of DNA synthesis (interphase, early prophase) in spermatogonia type A and intermediate. The reason for the difference observed between dormant A irradiated with 50 and 100 R roentgen rays in stages III—IV and VI—VII, respectively, is possibly that the dormant A when irradiated in stage VI—VII are very close to the DNA synthesis preceding the first division of type A. If irradiated at stage III—IV the dormant A might have had time to recover.

It is evident from Figs. 1 and 2 that the most marked effect of ^{90}Sr occurred in the stages just discussed. The two dormant A types received, however, the same amount of damage, which seems to indicate that in the case of ^{90}Sr no recovery takes place. ÅBERG & GILLNER (1964) have shown that ^{90}Sr is located in the spermatozoa of rams treated with ^{90}Sr. It is therefore perhaps not too much to assume an incorporation of ^{90}Sr during an early stage of spermatogonial development. If incorporated in some vital molecules ^{90}Sr continues to give its damaging effect over a fairly long time. An observation

made earlier of the present authors (HENRICSON et coll 1962) is the insignificant effect of ^{90}Sr on the spermatogonia of type B which is contrary to the sensibility of these cells to roentgen and γ rays (OAKBERG 1957, MONESI 1962) A possible explanation for this might be that no incorporation of ^{90}Sr takes place in this stage and that the irradiation absorbed by the cells from the injected dose of ^{90}Sr is too small to exceed the limit of cell killing

The original purpose of this study was to estimate the radiation dose absorbed by testicular tissue after a given dose of ^{90}Sr The results suggest that three to five days after ^{90}Sr injection the irradiation dose corresponds to whole body irradiation with 12 R or 12 to 25 R However no precise relation can be given without further study of the complicated functional and morphological effects induced by ^{90}Sr and which change from stage to stage in the development of the cells in the germinal epithelium

SUMMARY

The effect of Sr (0 7 μCi/g bodyweight) on different types of spermatogonia in mice is compared to total body irradiation of 12 25 50 and 100 R roentgen rays the strontium dose used apparently corresponding to 12 R or 12 to 25 R roentgen rays When irradiated before the DNA synthesis of A spermatogonia stage VIII the strontium effect is greatest and a comparison with the roentgen effect of most interest

ZUSAMMENFASSUNG

Der Wirkungseffekt von ^{90}Sr (0 7 μCi/g Korpergewicht) auf die verschiedenen Arten der Spermatogenese bei Mausen wird mit dem Effekt einer Totalbestrahlung von 12 25 50 und 100 R verglichen Die Strontiumdosis scheint einer Rontgendosis von 12 bis 25 R zu entsprechen Der Strontiumeffekt ist am grossten wenn die Spermatogonien A Stadium VIII bevor der DNS Synthese bestrahlt werden und dann wird ein Vergleich mit dem Roentgeneffekt auch von grosstem Interesse

RÉSUMÉ

Les auteurs ont comparé l effet du Sr (0 7 μCi/g de poids corporel) sur differents types de spermatogonies de la souris a l effet de l irradiation de tout le corps par 12 25 50 et 100 R de rayons roentgen la dose de strontium administree correspondant apparemment à 12 R ou 12 a 25 R de rayons roentgen C est quand il intervient avant la synthese de l ADN des spermatogonies A stade VIII (de OAKBERG) que l effet du strontium est maximum et que sa comparaison avec l effet des rayons roentgen présente le plus d intérêt

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MELPHALAN (L PHENYLALANINE NITROGEN MUSTARD) TREATMENT IN MYELOMATOSIS

Report of 46 cases

by

TORSTEN NORIN

The results of treatment of myelomatosis have to date been rather disappointing A small number of cases with solitary lesions (plasmocytoma) may be successfully treated with local ionizing radiation but when the disease is generalized as in multiple myeloma the possibilities of the method are very limited It is often possible to keep the subject in good health for some time with local roentgen therapy but the effect is generally of short duration

It would appear desirable in the generalized form of the disease to treat the patient with a drug affecting the tumour areas of the whole body Such methods have been tried with varying results The use of stilbamidin which can be demonstrated in the myeloma cells during the treatment has certain unwanted side effects and has resulted in less use of this drug

Urethane has been preferred up to now in myelomatosis This drug was first used with good results in multiple myeloma by ALWALL Its greatest

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disadvantage, however, is that its tolerance in adequate doses is difficult and gastrointestinal disorders generally make it necessary to withdraw the treatment before satisfactory results have been obtained

Different alkylating agents of nitrogen mustard type with tumour inhibiting effect have also been tried in the treatment of myeloma The use of the original nitrogen mustard has not, however, had any success Different newly synthesized agents of the alkylating type have been tried in this disease There are, above all, two very effective drugs, phenylalanine mustard and cyclophosphamide (endoxan, Cytoxan) Good effects from treatment with the latter drug has been reported by e g SCHUMACHER et coll and RIVERS et coll

BLOKHIN et coll, among others from Russia, have reported good results in the treatment of myeloma by an agent called sarcolysine, DL phenylalanine mustard BERGEL & STOCK, at the Chester Beatty Research Institute, synthesized the L isomer of the same compound and it was possible to show that this isomer had a better effect on tumour tissues than the DL isomer of the same compound (BERGEL & STOCK, KOLLER & VERONESI) It therefore seemed worth trying L phenylalanine mustard, melphalan p di (2 chloroethyl) amino L phenylalanine now manufactured by Burroughs, Wellcome & Co, under the name Alkeran, in the treatment of myelomatosis

BERSAGEL et coll, WALDENSTROM, and SPEED et coll have reported good results with melphalan in the treatment of myelomatosis during the last three years

Material Patients with multiple myeloma, in order to obtain sufficient material in a reasonably short time, have been treated with melphalan (supplied by Chester Beatty Research Institute) in five clinics at five different Swedish hospitals (1) King Gustaf V Jubilee Clinic (Prof M Strandqvist) at the University of Gothenburg (22 cases), (2) King Gustaf V Jubilee Clinic (B Ebenius and Prof M Lindgren) at the University of Lund (6 cases), (3) the Radiotherapy Clinic (I Gynning) at Malmo Allmanna Sjukhus (2 cases), (4) the Radiotherapy Clinic (B Mansson and T Norin) at Central lasarettet, Gavle (15 cases), and (5) the Medical Clinic (E Segerdahl and G Haggblom) at Lasarettet, Bollnas (1 case)

The treatment of the first cases was started in 1958 and the preliminary results were reported by NORIN (1964) The material consisted of 46 cases, 31 males and 15 females, in all of which a clear clinical diagnosis with positive marrow puncture, or histo pathologic diagnosis and pathologic electrophoretic pattern as well, were obtained

Melphalan was the only treatment used in 18 cases 23 of the other cases received roentgen treatment in one or several series, or treatment with another

Table

Record of causes for discontinuing the melphalan treatment as related to the classification in three groups

	Lack of cooperation	Leukopenia (L)	Trombocytopenia (T)	L + T	Progress	Still under treatment
Objective and subjective improvement	—	4	3	1	2	5
Subjective improvement alone	1	—	4	1	4	1
No effect	1	7	2	4	7	—

One patient is still alive two months after discontinuing the treatment

chemotherapeutic agent before the melphalan treatment Roentgen treatment to prevent fracture was in 5 cases given at the same time as the melphalan treatment (the locally obtained roentgen effect was not registered as an improvement) In four of these five cases no objective or subjective effect could be recorded from the melphalan treatment One of the cases belongs however to the group of objective and subjective improvement The melphalan treatment was given to this case in several series the irradiation being administered concurrently with the first melphalan series the objective effect from the melphalan treatment could later be observed in a subsequent series in which no radiation was given

Method Melphalan was given perorally, in doses of 4 to 6 mg (0 05 to 0 1 mg/kg bodyweight), initially every day for 10 to 15 days, then every second day and after about a month the dosage was reduced so that it was first given twice and then once a week This dose was maintained for as long as possible Repeated blood controls (white blood cells and platelets) were made during the treatment time In four of the earliest cases the treatment was given in series initially 4 to 6 mg/day up to a total dose of 100 mg, repeated at intervals when pain returned The highest total dose was 758 mg (10 8 mg/kg body weight) given during a treatment period of 3 years and 8 months The average dose was in cases with objective and subjective improvement 373 mg (6 2 mg/kg bodyweight), in cases feeling only slightly better 391 mg (6 5 mg/kg bodyweight) and in cases without effect 143 mg (2 7 mg/kg bodyweight)

Results

The effects of treatment as relief from pain subjective improvement (or symptoms) or objective improvement (signs) were recorded It was sometimes possible to observe a decrease in the number of plasma cells at marrow

puncture but, as it is often difficult to obtain comparable punctures from bone marrow in myelomatosis, this decrease has not been registered as an objective improvement. The relief from pain was always striking.

Objective regression was constantly associated with subjective improvement and was registered in 15 out of the total of 46 cases. In addition to these, subjective improvement alone was registered in another 11 cases, and no improvement, either subjective or objective, was noted in the remaining 20 cases.

Evaluation of the melphalan treatment. The record of 'objective improvements' (in all 15 cases) comprised the following treatment results:

1. Decrease of pathologic serum fraction in electrophoresis (11 out of the 15 cases). The average decrease was 1.9 g % (6.1 to 0.5), in seven cases with hyperproteinemia a decrease to normal values could be observed at the same time. The average decrease was 3.0 g % (7.2 to 0.7) (see Fig. 2).

2. Recalcification of bone lesions (2 out of 15 cases). Definite recalcification of bone lesions was recorded in two cases, in one of these CEDERQVIST & LIDÉN have shown that after the treatment with melphalan the retention of ^{85}Sr, measured by total body counting, was considerably increased.

3. Regression of tumour (2 cases). Palpable tumours completely disappeared in two of the cases treated.

4. Regression of signs of compression of the spinal cord (2 cases). Two patients with total paralysis of the legs regained their power of movement, the reflexes became normal, and the bladder and bowel functions were restored.

5. Decrease of proteinuria (4 cases). A lasting decrease in the proteinuria, average 11 ‰ (9.7 to 12 ‰) was recorded in these four cases. In no case, however, was any decrease in the NPN recorded.

6. Decrease in plasma cell count in the peripheral blood (1 case). In this case, in which the plasma cell count of the peripheral blood was high, the percentage was decreased from 11 to 0.5 %.

7. Increase of the haemoglobin value (3 cases). The increase was definite, on the average 2.5 g % (1.1 to 3.4).

The duration of the remission obtained by the treatment has varied from a fortnight to 48 months (Fig. 1). In 6 of the 15 cases with an 'objective improvement' the remission has lasted for more than a year, in 3 of the cases more than two years, and in one case more than three years, five of these 15 cases are still under treatment. The average duration of remission in the group of 'objective and subjective improvement' was 13.1 months against 10.5 months in the group of cases in which only subjective improvement was recorded.

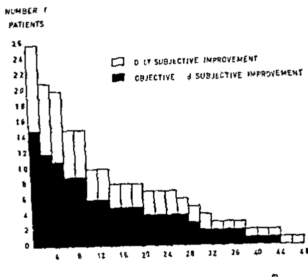


Fig 1 Duration of remission obtained in the treatment

Effect of the melphalan treatment on different immunologic types Immuno electrophoresis was performed in 25 of the 46 cases treated Fifteen of these belonged to the gamma group and ten to the B_2A group

	Immunologic type	
	$\gamma A(\beta_2 A)$	$\gamma G(\gamma)$
Objective and subjective improvement	5	4
Only subjective improvement	1	2
No effect	4	9
	10	15

The number of cases is too small to permit any definite conclusions There is however a tendency to obtain better results from melphalan treatment of an immunologic γA type

Complications Like all tumour inhibiting agents of this alkylating type melphalan has a depressing effect on the bone marrow A slight reduction in the haemoglobin value occurs in some cases but the most predominant bone marrow complication is an important effect on leukocytes and trombocytes Leukopenia ($<$ 2 000 white blood cells/mm³) and trombocytopenia ($<$ 100 000 trombocytes/mm³) alone or both together often appear during the

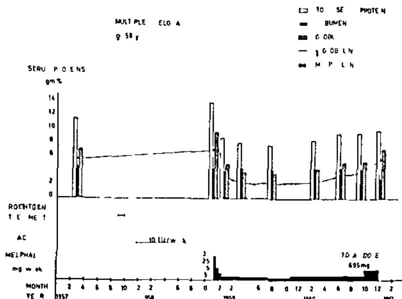


Fig 2 Case 1 Time relations and effect on sedimentation rate electrophoresis and pathologic protein fraction

treatment and this complication is the most common cause of its suspension (see Table)

Leukopenia, trombocytopenia, or both, have forced a discontinuation of the treatment in 26 out of the total of 46 cases The leukopenia or trombocytopenia has however never been so severe as to have caused death through agranulocytosis or haemorrhage It has sometimes been possible to resume the melphalan treatment after a short interval (among others with two of the cases that received treatment in series)

Leukopenia or trombocytopenia has appeared on an average of 10 months from the beginning of treatment in the group of objective and subjective improvement but as early as four months in the other groups, i e cases with only subjective improvement as against no improvement

Severe generalized itching without obvious dermal changes was recorded in one case

Case reports

Case 1 Female aged 58 with a confirmed gamma myeloma and positive marrow puncture was earlier given roentgen treatment for a bone lesion in a vertebra and later ACTH therapy Time relations and effect on the sedimentation rate electrophoresis and pathologic protein fraction are indicated in Fig 2

The patient was bedridden due to pain when treatment began but after four weeks treatment the pain completely disappeared and she was able to return to her work as a shop assistant She afterwards had small and continuous doses of melphalan while continuing with her

occupational work but after 22 months of treatment the disease flared up again and she quickly succumbed

Case 2 Female aged 84 with a three year-old history of myelomatosis Electrophoresis revealed a gamma myeloma and marrow puncture typical signs of myelomatosis On admission the patient had an egg sized tumour adherent to the sternum paralysis of both legs paralysis of the urinary bladder and loss of bowel function Roentgen examination revealed total destruction of L4

The patient received 100 mg melphalan over 20 days and the paralysis and disturbances of bladder and bowel function disappeared completely as did the palpable tumour over the sternum

Decrease in the pathologic gammafraction and roentgen examination one year later revealed that the affected part of L4 was mostly recalcified

Further improvement occurred after a new series of treatments with a total dose of 100 mg melphalan but later deterioration could not be prevented and the patient died one year and four months after the beginning of the first melphalan treatment

Discussion

Phenylalanine—nitrogen—mustard (melphalan) has been used in the treatment of myelomatosis in 46 cases with relief of pain in 26, and objective improvement in 15 cases results that are extremely satisfactory according to BERGSAGEL et coll WALDENSTROM and SPEED et coll

Similar results have been obtained with other drugs Cyclophosphamide for example, seems primarily to give the same effect as melphalan but in two cases which had previously improved with cyclophosphamide it was possible to produce further remission with melphalan

A depression of the bone marrow follows treatment with melphalan, as with other alkylating agents but this has never been very marked One of the cases treated with melphalan however, developed a severe but transient itch all over the body with no visible dermal signs It could not be decided whether this was caused by melphalan or some other pain relieving drug and this complication had therefore to be included

The pain relief obtained has often been striking and several patients, bedridden because of pain have gradually been able to resume work the effect has often been long standing Ten out of 26 cases have had almost complete relief from pain for more than a year 8 cases for more than 2 years and 3 cases more than 3 years

In 4 of the earliest cases treated the drug was given in several series with a total dose of about 100 mg melphalan in each and in daily doses of 4 to 6 mg In the other 42 cases the treatment was administered for as long as possible with successively decreasing doses and with a maintenance dose which after about a year was 2 to 4 to 6 mg/week (0 03 to 0 1 mg/kg bodyweight)

The author considers this form of continuous treatment the most worth while as in this way the growth activity is inhibited by the constant influence of the tumour depressing agent

SUMMARY

Forty six cases of verified myelomatosis treated over a long period with melphalan perorally with good effect, are reported The objective and subjective results recorded in 15 cases and the complications that were encountered are discussed

ZUSAMMENFASSUNG

Der Bericht umfasst 46 Falle von bestatigter Myelomatose die fur lange Perioden oral mit Melphalan mit gutem Resultat behandelt wurden In 15 Fallen werden die objektiven und subjektiven Resultate sowie die angetroffenen Komplikationen beschrieben

RÉSUMÉ

Présentation de quarante six cas de myélomatose vérifiée traités pendant une longue période par le melphalan par voie buccale avec de bons résultats I auteur rapporte les résultats objectifs et subjectifs dans 15 cas et examine les complications

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FROM THE DIVISION OF RADIOBIOLOGY RESEARCH INSTITUTE OF NATIONAL DEFENCE SUNDBYBERG AND THE DEPARTMENT OF PHARMACOLOGY ROYAL VETERINARY COLLEGE STOCKHOLM SWEDEN

DISTRIBUTION OF YTTRIUM 91 IN MICE STUDIED BY WHOLE BODY AUTORADIOGRAPHY

by

LARS ERIK APPELGREN ARNE NELSON and SVEN ULLBERG

Among the fission products formed in a reactor and in nuclear weapons are *several isotopes* of yttrium (KYKER 1962) As yttrium 90 is a daughter of strontium 90 this radionuclide also contributes to the body burden after *ingestion of* ^{90}Sr When considering the problems of the internal radiation the relatively long range of the ^{90}Y betas should be remembered (max energies ^{90}Y 2 24 MeV ^{90}Sr 0 61 MeV) In this connection it is also of interest to know whether *or not the* ^{90}Y found in the body as a daughter product of ^{90}Sr is relocalized away from the strontium deposit sites

The distribution in the body of yttrium is also of importance from a hygienic viewpoint in relation to its *industrial use* and because of its therapeutic use for local irradiation especially of tumours covering membranes of the body cavities (WALKER 1964) A *review* article on the metabolism of radioyttrium was published by Eileen RAMSDEN (1961)

In the present work the distribution of ^{91}Y in mice has been studied by whole body autoradiography and it was chosen because its radiation properties

Submitted for publication 23 February 1965

The author considers this form of continuous treatment the most worth while as in this way the growth activity is inhibited by the constant influence of the tumour depressing agent

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Forty six cases of verified myelomatosis treated over a long period with melphalan perorally with good effect, are reported The objective and subjective results recorded in 15 cases and the complications that were encountered are discussed

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Présentation de quarante six cas de myélomatose vérifiée traités pendant une longue période par le melphalan par voie buccale avec de bons résultats L'auteur rapporte les résultats objectifs et subjectifs dans 15 cas et examine les complications

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LARS ERIK APPELGREN, ARNE NELSON and SVEN ULLBERG

Among the fission products formed in a reactor and in nuclear weapons are several isotopes of yttrium (KYKER 1962). As yttrium 90 is a daughter of strontium 90, this radionuclide also contributes to the body burden after ingestion of ^{90}Sr. When considering the problems of the internal radiation the relatively long range of the ^{90}Y betas should be remembered (max. energies ^{90}Y 2.24 MeV, ^{90}Sr 0.61 MeV). In this connection it is also of interest to know whether or not the ^{90}Y found in the body as a daughter product of ^{90}Sr is relocalized away from the strontium deposit sites.

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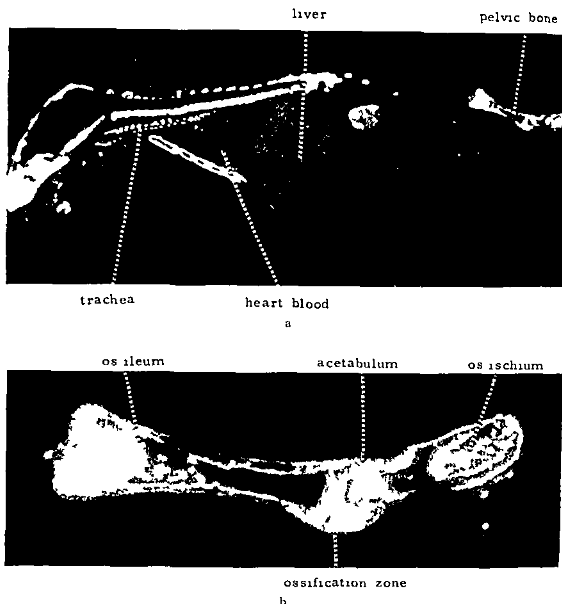
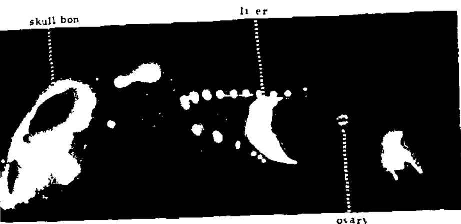
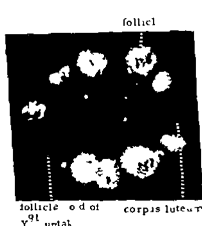


Fig. 1. a) Autoradiogram showing the distribution of ^{91}Y one hour after injection. White areas correspond to high radioactivity. No detectable ^{91}Y left in the blood; the uptake is highest in the skeleton and in the tracheal cartilage; a slight accumulation can also be seen in the blood vessel walls, liver and kidney. b) Detail of (a). In the pelvic bone high concentration in ossification zones and in periosteal and endosteal layers.

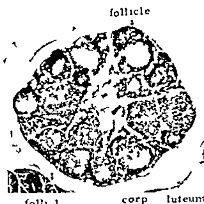
(1.55 MeV betas, half life 57 days) are more favourable for autoradiography than are those of ^{90}Y. Chemically, yttrium is closely related to the lanthanides. Distribution investigations of certain lanthanides using the same autoradiographic technique have been published earlier (EWALDSSON & MAGNUSSON 1964).



a



b



c

Fig. [illegible] a) Autoradiogram of Y in non pregnant mouse 2 hours after injection. Uptake of radioyttrium only in skeleton, liver and ovary. b) Autoradiogram of ovary. High concentration in the walls (apparently mainly in the granulosa layer) of most but not all follicles. c) Section stained with hemalum eosin corresponding to the ovary autoradiogram.

Methods. Carrier free ^{91}Y was obtained from the Radiochemical Centre, Amersham, England. The isotope was delivered in 1 N hydrochloric acid. The pH was adjusted to 2—2.5 before injection by addition, drop by drop of 0.1 N sodium hydroxide and checking the pH with very small strips of indicator paper (Merck 0.5—5.0). Below pH 2.5 yttrium is ionic.

Fourteen CBA mice were injected intravenously in a tail vein with a single dose of ^{91}Y corresponding to approximately 1 μCi/g bodyweight. Six of the

mice were pregnant in late gestation state They were killed at the following times after injection 5 min, 20 min, 1 hour, 4 hrs, 24 hrs and 96 hrs Four male and 4 female adult mice were also injected They were killed 5 min, 20 min, 2 hrs, and 24 hrs, respectively, after injection The autoradiographic technique has been described in detail previously (ULLBERG 1954, 1958) Sectioning, drying and exposure were carried out at —10°C Twenty micron thick *sagittal sections were taken at various levels* The sections were freeze dried and pressed against 'Structurix (Gevaert) X ray' film After exposure ranging from 2 to 15 days the roentgen films were developed and some of the corresponding sections stained (while still kept on the tape)

Results

The radioactivity gradually disappeared from the blood, a process which was largely completed after 4 hours Part of the ^{91}Y was excreted, mainly through the kidneys and the bulk of the remaining portion was taken up in the skeleton, where it remained throughout the experiment (4 days) In addition, some soft tissues also showed a slight tendency towards specific uptake and retention of the radioyttrium The soft tissues that showed the highest concentrations were kidneys, ovaries, gastric mucosa, mammary glands and parts of the placentae A more detailed description of the distribution pattern is given below

Skeleton Within the bones the highest uptake was seen in the epiphyseal mineralisation zones and subperiosteally In the fetuses, where localization was seen exclusively in the skeleton (Fig 3), the highest uptake is also found in the epiphyses

Cartilage In the adult mice, uptake was seen in the cartilage of the trachea, ribs and ear In the fetal bones, however, no uptake of ^{91}Y in the cartilage could be observed (see Fig 3)

Myocardium and blood vessels The myocardium in all time intervals studied, had a slightly higher activity than the skeletal muscles In addition to a homogenous distribution a few very hot spots were seen The walls of the large arteries (e g aorta and the pulmonary artery) were very accentuated

Kidney The main path of excretion of yttrium seems to be through the kidneys Five minutes after the injection, the kidney showed a rather strong radioactivity fairly evenly distributed indicating a rapid onset of excretion Two

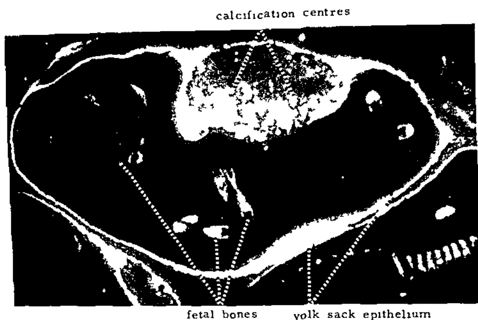


Fig 3 Detail of whole body autoradiogram of pregnant mouse 4 hours after injection of Y showing part of uterus Selective localization in the bones of the fetus especially in the epiphyseal ossification zones no uptake in the epiphyseal cartilage is detectable Strong uptake also in the yolk sac epithelium and in degenerative calcification centers in the chorioallantoic placenta

hours after the injection the distribution in the cortex was spotty This persisted throughout the investigation The urinary bladder showed a very high amount of ^{91}Y in the first 4 hours of the experiment followed by a slight decrease

Digestive system The liver showed intermediate activity and no apparent excretion through the bile could be detected The gastric mucosa showed a very strong uptake with a mostly spotty pattern in all the time intervals studied The isotope concentration of the intestines was very low both in the walls and in their contents with the exception of some scattered hot spots

Lungs In some animals scattered hot spots could be seen in the lungs probably due to radiocolloid formation

Ovaries The ovaries rate among the soft tissues which show the highest uptake in the body The strongest accumulation was in the follicle walls of the non pregnant females (Fig 2b) No specific accumulation was seen in corpora lutea

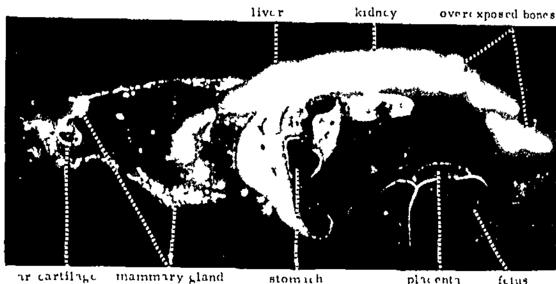


Fig. 1. Autoradiogram of a sagittal section from the lateral portion of a pregnant mouse 4 days after injection of ^{91}Y. The film is partly overexposed from ^{91}Y in bones. Specific uptake can also be seen in the kidney, gastric mucosa, liver, mammary glands, fetal membranes and placenta.

Testes. No specific localisation in the testes.

Mammary glands. The mammary glands of the pregnant mice showed a strong uptake, apparently confined to the parenchyma of the gland.

Placentae. The chorioallantoic placenta showed a slight uptake of evenly distributed ^{91}Y which could be seen also after the blood activity had disappeared. A few localized areas with very strong uptake of radioyttrium, corresponding to sites of degenerative calcification, were also observed. Outlining the chorioallantoic placenta on the maternal side, a spotty line of high uptake was seen. On the fetal side of the chorioallantoic placenta, a very strong accumulation was noted, probably higher than in any other soft tissue and apparently confined to the yolk sac epithelium.

Discussion

The distribution picture was dominated by the uptake in the skeleton but the hard tissue localization was not selective, as a few other organs also took up and retained ^{91}Y, although to a lower degree.

When the distribution pattern is compared with the pattern obtained in similar autoradiographic investigations with ^{90}Sr (NILSSON & ULLBERG) it can be noted that radiostrontium rapidly and exclusively was taken up by the skeleton. No tendency of the radioactive material to reappear in any soft

tissues indicating a relocalization of the ^{90}Y formed in the body as a ^{90}Sr daughter could be noticed not even long after ^{90}Sr injection or in heavily overexposed autoradiograms

The autoradiograms of yttrium in bone did not differ significantly from those of calcium (ULLBERG 1963) and strontium The radioactivity was in all cases localized in epiphyseal growth lines This was especially accentuated in the fetal bones

RAMSDEN (1961) has suggested that the tendency to localize in soft tissues is dose dependent tracer doses being more exclusively localized to bones In the present work however a soft tissue localization was observed although a tracer dose was given

RAMSDEN also claimed that with a larger dose radiocolloid formation is relatively increased and that the radiocolloid is responsible for the soft tissue localization In our work the autoradiographic pattern shows a partially even distribution and a partially spotty localization

The initial accumulation in the kidney obviously can be related mainly to excretion but the spotty uptake in the renal cortex is apparently due to specific retention in the walls of the renal tubules A similar renal tubular uptake has been observed also for ^{203}Hg and cadmium The uptake of activity in the gastric mucosa was remarkably high

Concerning the radiation hazards of yttrium taken up by the body the strong uptake in the follicular walls of the ovary deserves to be mentioned This may involve risks for beta radiation of the developing ova, with possible genetic consequences

The fetus seems to be fairly well protected as the placental transfer was partially blocked However some ^{91}Y passed the placenta and localized in fetal bones The intense accumulation in the yolk sac epithelim may be related to a fetal discrimination mechanism

Acknowledgement

The authors are indebted to Mr H Sundberg for excellent technical assistance

SUMMARY

The distribution of Y in mice was studied by means of whole body autoradiography Yttrium is predominantly taken up by the hard tissues with a localization similar to that of strontium In addition some soft tissues such as renal cortex ovaries gastric mucosa and in pregnant animals the mammary glands and parts of the placenta show a specific uptake Of especial interest is the strong concentration in the follicular walls of the ovaries with possible genetic consequences The fetal uptake is relatively limited and concentrated to the fetal skeleton

ZUSAMMENFASSUNG

Die Untersuchungen zeigen dass Yttrium 91 hauptsachlich von den harten Geweben aufgenommen wird wobei es *ahnlich dem Strontium gelagert* wird Spezifische Speicherung fand in einigen weichen Geweben wie Nierenrinde Eierstocke, Magenschleimhaut und bei graviden Tieren in den Brustdrusen und Teilen der Plazenta statt Besonders interessant ist die *starke Konzentration in den Follikelwanden der Eierstocke* wobei genetische Folgen moglich sind Die Aufnahme durch den Foetus ist verhaltnismassig gering und auf das foetale Skelett beschrankt

RÉSUMÉ

Ces recherches ont montré que l'yttrium 91 est fixé principalement par les tissus durs avec une localisation semblable à celle du strontium On a constaté une fixation spécifique dans certains tissus mous tels que le cortex rénal les ovaires la muqueuse gastrique et chez les animaux gravides les glandes mammaires et des parties du placenta Particulièrement intéressante est la forte concentration dans les parois folliculaires des ovaires pouvant avoir des conséquences génétiques La fixation foetale est relativement limitée et concentrée sur le squelette foetal

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FROM RADIUMHEMMET (DIRECTOR PROF S HULTBERG), KAROLINSKA SJUKHUSET, STOCKHOLM SWEDEN

COMPLICATIONS IN RADIOIODINE TREATMENT OF HYPERTHYROIDISM

by

F EDSMYR and J EINHORN

The complications resulting from radioiodine therapy in cases of hyper thyroidism fall into two groups according to whether they occur within one month of treatment or later they may be referred to as initial and late compli cations respectively Initial complications are of two types namely a local reaction with swelling and tenderness of the thyroid gland and an exacerbation of hyperthyroidism Reactions of this type are extremely common but usually so mild as not to be noticed by the patient Even slight swelling of the thyroid may however be fatal in cases of large goitres and compression of the trachea Where there is marked hyperthyroidism or severe cardiac disease exacerbation can be particularly serious It seems likely that the initial reaction after ^{131}I treatment has sometimes been a cause of death (NELSON et coll 1952, LARSSON 1955 LAMBERG et coll 1959 WERNER 1962)

A large series of patients were followed up after ^{131}I treatment for hyper

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thyroidism and the initial and late complications observed in this series are reported, the mortality from initial complications is evaluated Part of this series, the 370 patients treated between 1951 and 1953, has been reported earlier (LARSSON 1955)

Material and Methods The series consisted of 2 035 patients — all those cases of hyperthyroidism treated by radioiodine from 1951 to 1961 The patients to receive radiotherapy were selected in collaboration with surgeons or internists, about half the number had been referred from the goitre clinic of the Surgical Department of St Erik's Hospital (Hj Wynbladh) The usual treatment was surgery for patients under 40 to 45 years of age, provided there were no contraindications Older patients were given radiotherapy with ^{131}I The mean age of the patients given radiotherapy was 62 years Of the whole series, 541 had no palpable goitre, 811 had diffuse enlargement of the thyroid gland and 683 had nodular goitre

The radioiodine dose was chosen according to the size of the thyroid gland — as judged by palpation and scintigraphy — and to the 24-hour uptake and effective half life of the radioiodine in the gland The intended radiation dose for the gland was 5 000 to 12 000 rad, the lower doses being given to younger patients who showed little if any thyroid enlargement The highest doses were administered to patients with nodular goitre

The patients were followed up regularly every 2 to 4 months during the year following treatment, and then every 6 to 12 months If necessary, another dose of radioiodine was given, usually 3 to 8 months after the earlier treatment Altogether 3 482 treatments were given to these 2 035 patients All but 14 of the survivors were observed for at least 2 years after the first treatment, most of the 14 patients (0 5 %) who were not available for follow up had left the country

The monthly mortality rate was calculated in relation to the time when the last ^{131}I treatment was given All the patients dying within one month after ^{131}I therapy were subjected to autopsy

Results and Discussion

Out of 2 035 patients receiving 3 482 treatments 9 died within one month of treatment, giving a mortality of 0 3 % Since the patients selected at this hospital for radioiodine therapy are usually among the older ones or have complicating diseases, some deaths from causes other than thyroid disease could be expected during the period in question

The mortality in the first month of treatment was by chance the lowest

Table

Patients dying within 30 days of ^{131}I treatment for hyperthyroidism — all patients were autopsied

Year of death	Age	^{131}I Dose	Time in days between treatment and death	Cause of death
19.6	63	First	8	Initial reaction
1954	70	First	12	Initial reaction
1955	67	Third	14	Initial reaction
19.4	80	First	5	Cerebral hemorrhage
19.4	63	First	29	Cerebral hemorrhage
1960	56	Second	8	Cardiac infarction
1961	61	First	17	Acute encephalomyelitis
1960	59	First	2?	Carcinoma of pancreas
1959	6?	Third	6	Carcinoma of gallbladder

monthly figure during the first 6 months after treatment as may be seen from the data given below

Period after last ^{131}I treatment	≤ 1	1—2	2—3	3—4	4—5	5—6 months
Number of deaths	9	12	13	9	11	18

During the first 18 months on an average 9 5 patients died every month which corresponds with the mortality during the first month It is not possible from the above figures or from any similar collations to draw any conclusions as to the mortality from the initial reaction

From the reports of the individual cases (see Table) it was found that of the 9 patients dying within one month of radioiodine therapy three had died with signs that suggest an exacerbation after treatment as cause of death they were classified as dying from the initial reaction in three other patients the reaction to the treatment may have been a contributory cause of death, two died from cerebral haemorrhage and one from myocardial infarction in a further three patients the treatment can hardly have been a contributory cause of death since two died from abdominal carcinoma known before the ^{131}I treatment was begun and the third from acute encephalomyelitis

Patients with large goitres severe hyperthyroidism or heart disease are not treated as out patients It was noted however that the initial reactions if present always appeared within 7 days of treatment A week in hospital is in most cases sufficient and if no deterioration is observed at this time there seems to be little likelihood of severe reactions occurring later on When

radioiodine treatment is followed by severe reactions — whether swelling of the gland or exacerbation of hyperthyroidism — the current routine treatment at this hospital consists of giving large doses of cortisone This usually has a dramatic effect *within an hour of the injection The doses are 100 to 150 mg* of cortisone acetate two or three times daily for 3 to 6 days, a longer period is seldom necessary Since this management of the initial reactions was introduced, there has been no death ascribable to the early complications of therapy, that is, not in the 1 239 cases treated since 1956 (see Table)

Possible complications after a long interval are late hypothyroidism, recurrence of hyperthyroidism and hazards of radiation, such as induction of thyroid carcinoma and leukemia, and genetic damage

The incidence of hypothyroidism occurring long after the ^{131}I treatment *was studied in the first 796 cases treated from 1951 to 1956 (BELING & EINHORN 1961) Of these patients, 99 6 % were followed up for at least two years* Hypothyroidism within one year of treatment occurred in 7 5 % Each year there after hypothyroidism developed in a further 3 % of the patients followed up so that the incidence after 7 years was about 27 % The curve shows no tendency to level off during the follow up period, and, to judge by its course, the incidence of hypothyroidism will rise further with time (DUNN & CHAPMAN 1964) Hypothyroidism is not a severe complication, being easy to control by thyroid substitution therapy Nevertheless, this late hypothyroidism *overtakes the patient very slowly and it is important to carry out periodic* checks so that substitution therapy can be started when necessary If such control cannot be performed, the patient should be informed about the symptoms of this common complication so that he may recognize them if they appear

Because the thyroid function has a tendency to diminish even long after treatment, the incidence of recurrence of hyperthyroidism following radioiodine treatment is very low it was only 0 4 % in the patients who were euthyroid for one year after ^{131}I treatment (BELING & EINHORN)

Progressive exophthalmus was observed in about 1 % of patients after ^{131}I treatment for hyperthyroidism

There is no patient with thyroid carcinoma or leukemia in this series of about 2 000 patients observed for 2 to 13 years It would seem from the present and earlier series that were followed up for up to 20 years (DUNN & CHAPMAN 1964) that morbidity *from thyroid carcinoma and leukemia (POCHIN* 1960, WERNER et coll 1961) in adults receiving ^{131}I treatment for hyper thyroidism is of little significance For some reason there were fewer thyroid tumors among adults receiving radioiodine therapy than might have been expected on the basis of chance However, the younger the patients the

greater the risk and as the age at which the treatment is given decreases the risk probably increases (SHELINE et coll 1959, 1962 STARR et coll 1964) It is well established that external roentgen irradiation of the thyroid gland in childhood increases the incidence of thyroid carcinoma (CLARK 1955, SIMPSON et coll 1955 WINSHIP & ROSVOLL 1961) and there is no reason to believe that the radiation delivered by radioactive iodine differs in its biologic effect

The observation time is at present too short for an assessment of the genetic risks and so long as these are unknown surgery should remain the method of choice in patients of fertile age with hyperthyroidism If the radiation dose received by the gonads is put at 0 5 rad/mCi of ^{131}I administered (MEANS et coll 1964) the gonadal dose in radioiodine treatment of hyperthyroidism with moderate enlargement of the thyroid gland is comparable with the dose given at two urographic examinations (LARSSON 1958) The gonadal dose at urethrocystography or hysterosalpingography (LARSSON 1958) is often higher than at ^{131}I treatment for hyperthyroidism However this does not justify radioiodine treatment for young patients as a routine method

Acknowledgement

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SUMMARY

Early and late complications of the ^{131}I treatment of hyperthyroidism were examined in 2 035 patients 99 5 % of whom were followed up for from 2 to 13 years The initial reactions to the administration of ^{131}I and the treatments for them are discussed the mortality is evaluated

ZUSAMMENFASSUNG

In gesamt wurden 2 035 Patienten auf die frühen und späten Folgen der ^{131}I Behandlung bei Überfunktion der Schilddrüse untersucht 99 5 % der Patienten wurden auf 2 bis 13 Jahre nachuntersucht Die unmittelbare Reaktion auf die Behandlung mit ^{131}I sowie die Behandlungsweise werden diskutiert und die Mortalität wird ausgewertet

RÉSUMÉ

Les auteurs ont étudié les complications précoces et tardives du traitement par ^{131}I de l'hyperthyroïdie chez 2 035 malades dont 99 5 % ont été suivis de 2 à 13 ans Ils examinent les réactions initiales à l'administration de ^{131}I et leur traitement et évaluent la mortalité

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FROM THE DEPARTMENT OF RADIOLOGY (DIRECTOR PROF S Y KIM), KYUNGPOOK NATIONAL UNIVERSITY SCHOOL OF MEDICINE TAEGU, KOREA

BLOOD FLOW CHANGES IN MUCOSA OF EMPTY AND DISTENDED CANINE AND HUMAN STOMACHS

by

SOON YONG KIM and WON HYUNG WOO

It is well known that the incidence of gastric carcinoma in the Koreans and the Japanese is much higher and that the younger age group is more involved than in other races (11 12 14) Various etiologic factors have been suggested without definite conclusions being reached SEGI et coll (1957) reported that rice or other cereals irritative foods and drinks or certain condiments seem to bear no relationship with the high incidence of gastric carcinoma in the Japanese although it was remarkably higher among big eaters and lower among small eaters KIM & JAKOBSSON (1962) suggested that a certain degree of gastric distension may alter the normal well balanced physiology of a part of the stomach and predispose to carcinoma or other diseases They investigated the quantitative blood flow in the mucosa of the empty and distended rat stomach and found that when the stomach was distended beyond a certain point the blood flow in the antral mucosa decreased significantly more at the lesser curvature than at the greater curvature

The present authors extended the research to determine whether the same phenomenon would occur in the human stomach as well as in the canine

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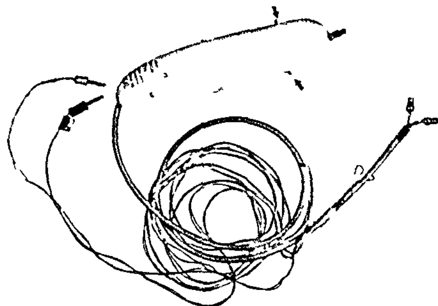


Fig 1 Thermistor balloon. The arrows indicate thermistors fitted onto the inner surface of a latex rubber balloon.

stomach. They have developed a device that accurately measures the temperature of the gastric mucosa to 0.01°C and records the change of the mucosal temperature as the stomach is distended to various degrees. The device consists of an intragastric balloon to which small thermistors are attached so that when the balloon is inflated the thermistors make contact with the surface of the gastric mucosa.

Materials and Methods

Measurement of the temperature of the gastric mucosa. One or two of the pinhead sized tiny Fenwal thermistors, type G 148, were fitted onto the inner surface of a latex rubber balloon and connected by means of fine cables to an amplifier and galvanometer through the larger hole of the Miller Abbott tube (Figs 1 and 2).

The thermistor used has an electric resistance of about 2,000 ohm at about 20°C, the resistance decreasing as the temperature rises. Manganium line resistances were adapted so as to have electric resistances equal to those recorded when the thermistors were placed in 30° C, 37° C and 38° C constant temperature waterbaths calibrated to within 0.05° C. When these resistances were substituted for the thermistors, the ammeter indicated the temperatures

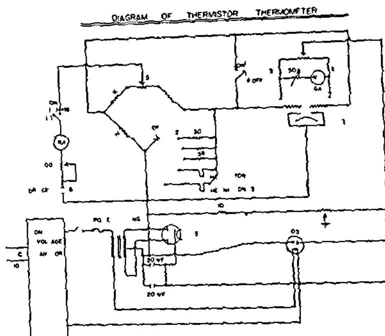


Fig 2 Diagram of thermistor thermometer

of 30 C 37° C and 38 C respectively The sensitivity of the ammeter was controlled so that its needle lay in a suitable position on the scale when the circuit was switched to the 3 and 4 positions (Fig 2) The sensitivity of this electric thermometer was made to show approximately a 3 cm needle deflection against a 1 C temperature difference so that 0 01 C temperature variation could be measured easily

Estimation of the degree of distension of the stomach The degree of distension of the stomach may be measured by the volume of air introduced or by the pressure inside the inflated balloon the authors however estimated the degree of distension by the area of the stomach as evident in roentgenograms The degree of the distension of the stomach was graded as minimal moderate, marked and extreme These, in canine experiments correspond to 60—80 cm², 100—120 cm², 140—160 cm² and over 200 cm² of the areas of the stomach, respectively (Fig 3) and in human experiments to 80—100 cm 140—160 cm², and over 200 cm² respectively with the exception of extreme distension which was omitted in order to avoid any possible discomfort to the subject (Fig 4)

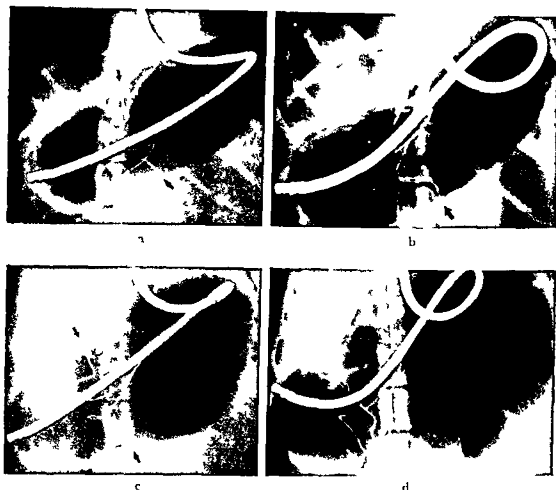


Fig 3 Dog No 7 Degrees of distension of stomach minimal (a) moderate (b) marked (c) and extreme (d)

Estimation of the temperature of the gastric mucosa Although the changes in the electric resistance with temperature usually take place within a few seconds, the galvanometer was read after it had become stabilized, usually at least 2 min after the stomach was inflated A delayed reaction due to the intervening balloon membrane between the gastric mucosa and the thermistor and the plastic membrane covering the thermistor was always considered possible The galvanometer was checked at 37° C and 38° C before the actual measurement of the temperature of the gastric mucosa, and thermistors 1 and 2 were then connected to the circuit The temperature of the part of the gastric mucosa to be examined was indicated by the deflection of the galvanometer

Because one scale of the galvanometer corresponded to 0 03 C, and about a quarter of the scale could be read, a temperature change as small as 0 008° C

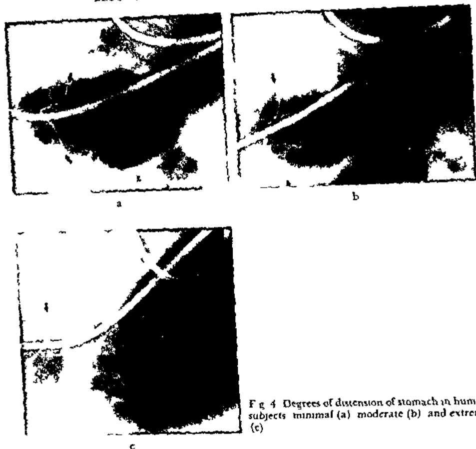


Fig 4 Degrees of distension of stomach in human subjects minimal (a) moderate (b) and extreme (c)

could be recorded The instability of the device precluded however figures below 0 01 C from being considered reliable

The cases in which the thermistors were incorrectly placed and remained at the lesser and greater curvatures of the stomach through the experiment or those in which the thermistors were thought not to be in contact with the gastric mucosa because of remnant fluid or air in the stomach were excluded

Experiments in dogs Healthy Mongorian dogs weighing 7 5 to 18 0 kg (mean weight 12 2 kg) and fasting overnight were used After the dogs had been anesthesized with penthothal sodium the thermistor balloon was inserted into the stomach the tip of the tube being placed at the pylorus under roentgen control The air and fluid contents of the stomach were removed through the tube to ensure that the balloon made contact with the gastric mucosa

Table 1

Degree of distension (increase) in 22 observations of the stomach of dog in supine position recorded in relation to the registered fall in temperature °C in the gastric mucosa — P indicates the significance level when compared with the temperature at minimal distension

Site	Lesser curvature			Greater curvature		
Degree of distension	Moderate	Marked	Extreme	Moderate	Marked	Extreme
Mean	0.07	0.17	0.29	0.01	0.04	0.06
Standard error	0.021	0.029	0.035	0.016	0.019	0.018
P<	0.01	0.001	0.001	0.6	0.05	0.01

The measurement of the temperature of the gastric mucosa was performed with four different degrees of distension of the stomach, i.e. minimal, moderate, marked and extreme, as already mentioned above, each measurement being repeated three times. Any difference in the temperature of the gastric mucosa produced by posture was observed by first taking a reading in the supine position and then in the right and left lateral positions.

The thermistor balloon was inflated as slowly as possible to avoid any sudden distension of the stomach and to lessen the influence of the temperature of the air introduced into the balloon, the galvanometer was read when the movement of the needle became stable. The experiments were performed with a small to a maximal degree of gastric inflation and each was repeated three times after the air had been removed.

Each experiment was carried out under roentgen control with roentgenograms to ensure the correct degree of inflation and the proper location of the thermistors.

Experiments in human subjects. Thirty four apparently healthy men, all of them fasting for more than 12 hours, without any history of abnormality of the digestive organs, were chosen at random. The experiment was carefully explained to the examinees beforehand. The thermistor balloon was swallowed in a sitting position and when the tip of the tube had passed into the stomach the examinee was laid on the roentgen table and the tip of the tube advanced to the pylorus. The procedure of the experiment was essentially the same as in the dog experiments except for the exclusion of an extreme degree of inflation of the stomach for the reason mentioned previously. There was no significant distress or complication during or after the experiment.

Table 2

Degree of distension (increase) in 7 observations of the stomach of dog in supine and left lateral positions recorded in relation to the registered fall in temperature C in the gastric mucosa — P indicates significance level when compared with the temperature at minimal distension

	Supine position						Left lateral position					
Site	Lesser curvature			Greater curvature			Lesser curvature			Greater curvature		
Degree of distension	Mod	Mark	Extr	Mod	Mark	Extr	Mod	Mark	Extr	Mod	Mark	Extr
Mean	0 11	0 22	0 33	+0 01	0 01	0 10	0 12	0 19	0 33	0 02	0 05	0 13
Standard error	0 037	0 067	0 033	0 008	0 022	0 028	0 019	0 034	0 047	0 079	0 079	0 036
P<	0 05	0 01	0 001	0 3	0 7	0 01	0 05	0 01	0 001	0 6	0 2	0 02

Only 6 observations

Results

Temperature of gastric mucosa examined in dogs in supine position The changes in the temperature of the gastric mucosa at the lesser and greater curvatures in the supine position according to the four graded degrees of gastric distension, are shown in Table 1 and Fig 5 As a matter of fact the temperature in each degree of gastric distension should be compared with that of the empty stomach but because of the difficulty in recognising whether the thermistors made good contact with the gastric mucosa or not in an empty stomach the temperature of the gastric mucosa at the minimal degree of gastric distension was taken as a standard Temperature fall or rise in this paper therefore means the temperature fall or rise from the temperature of the gastric mucosa at this minimal degree distension

The mean temperature fall at the lesser curvature at moderate marked and extreme degrees of gastric distension compared with a minimal degree were thus 0 07 C ± 0 021 C ($P<0\ 01$), 0 17 C ± 0 029 C ($P<0\ 001$) and 0 29 C ± 0 035 C ($P<0\ 001$), respectively and the degree of temperature fall became marked as the distension increased The fall of temperature at the greater curvature at moderate marked and extreme gastric distension were 0 01 C ± 0 016 C ($P<0\ 6$) 0 04 C ± 0 019 C ($P<0\ 05$) and 0 06 C ± 0 018 C ($P<0\ 01$) respectively The temperature fall at the greater curvature is much less than at the lesser curvature the former being only about a fifth of the latter

Temperature of the gastric mucosa examined in the left lateral position The fall of mean temperature in the left lateral position at the lesser curvature in cases

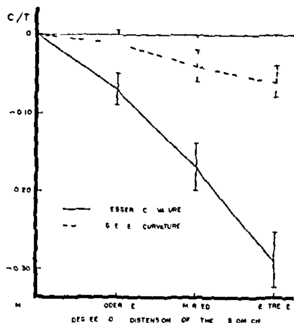


Fig 5 Fall in temperature (°C) in the mucosa of the dog with increase in the degree of gastric distension supine Bars indicate standard error

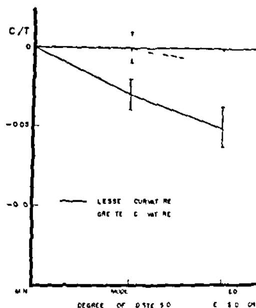


Fig 6 Fall in temperature (°C) in human gastric mucosa with increase in the degree of gastric distension with air supine Bars indicate standard error

of moderate, marked and extreme degrees of distension were 0.12° C ± 0.049° C ($P<0.05$), 0.19° C ± 0.054° C ($P<0.01$) and 0.33° C ± 0.042° C ($P<0.001$), respectively, while in the supine position they were 0.11° C ± 0.037° C ($P<0.05$), 0.22° C ± 0.062° C ($P<0.01$) and 0.33° C ± 0.053° C ($P<0.001$), respectively, (Table 2) These data suggest that the changes in temperature of the gastric mucosa do not alter with changes in the positions of the subject The same is true at the greater curvature The fall in mean temperature in the left lateral position when the stomach was inflated to the moderate marked and extreme degrees were 0.02° C ± 0.029° C ($P<0.6$), 0.05° C ± 0.029° C ($P<0.2$) and 0.13° C ± 0.036° C ($P<0.02$), respectively, while in the supine position the mean temperature rose by 0.01° C ± 0.008° C ($P<0.3$) when the stomach was inflated to the moderate degree and fell by 0.01° C ± 0.022° C ($P<0.7$) and 0.10° C ± 0.028° C ($P<0.01$) respectively when the stomach was inflated to the marked and extreme degrees

Temperature of the gastric mucosa examined in the right lateral position The fall in mean temperature at the lesser curvature in the right lateral position at moderate, marked and extreme gastric distension were 0.04° C ± 0.034° C ($P<0.3$), 0.17° C ± 0.069° C ($P<0.05$) and 0.27° C ± 0.077° C ($P<0.02$), respectively, while in the supine position the mean temperature rose by

Table 3

Degree of distension (increase) in 6 observations in stomach of dog in supine and right lateral positions recorded in relation to the registered fall or rise in temperature C in the gastric mucosa — P indicates the significance level when compared with the temperature at minimal distension

	Supine position						Right lateral position					
Site	Lesser curvature			Greater curvature			Lesser curvature			Greater curvature		
Degree of distension	Mod	Mark	Extr	Mod	Mark	Extr	Mod	Mark	Extr	Mod	Mark	Extr
Mean	*+0 01*	*0 18*	*0 25*	*0 03*	*0 06*	*0 07*	*0 04*	*0 17*	*0 27*	*0 02*	*0 04*	*0 02*
Standard error	0 025	0 061	0 088	0 050	0 056	0 050	0 034	0 069	0 077	0 054	0 065	0 043
P<	0 7	0 05	0 05	0 6	0 4	0 3	0 3	0 05	0 02	0 8	0 6	0 7

0 01 C ± 0 025 C (P<0 7) when the stomach was distended to a moderate degree and fell by 0 18 C ± 0 061 C (P<0 05) and 0 25 C ± 0 088° C (P<0 05) respectively when the stomach was distended to marked and extreme degrees Here again no significant difference in the temperature changes between the supine and right lateral positions was evident (Table 3)

The fall in mean temperature at the greater curvature in the right lateral position at moderate marked and extreme degrees of gastric distension were 0 02 C ± 0 054 C (P<0 8) 0 04° C ± 0 065 C (P<0 6) and 0 02 C ± 0 043 C (P<0 7) respectively while in the supine position they were 0 03 C ± 0 050 C (P<0 6), 0 06 C ± 0 056 C (P<0 4) and 0 07 C ± 0 050 C (P<0 3) respectively

Experiments in human subjects The changes in the temperature of the gastric mucosa according to the degrees of gastric distension in the supine position are shown in Table 4 and Fig 6 The mean fall in temperature of the mucosa at the lesser curvature at moderate and marked degrees of gastric distension were 0 03 C ± 0 009 C (P<0 01) and 0 05 C ± 0 012° C (P<0 001) respectively The temperature fall at the greater curvature was not so marked as at the lesser curvature that is the mean temperature remained the same when the stomach was moderately distended while the mean temperature fell by 0 01 C ± 0 011 C (P<0 4) in the marked degree of gastric distension this is not significant statistically The difference in temperature fall however between that at the lesser curvature and the greater curvature with a marked degree of distension was significant (P<0 05) These data suggest that the changes in temperature of the gastric mucosa in human subjects follows more or less the same tendency as observed in the experiments in canines

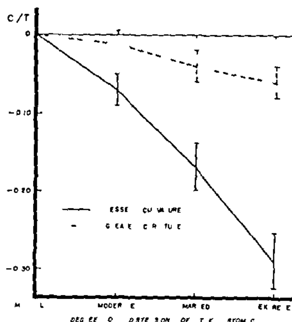


Fig 5 Fall in temperature (°C) in the mucosa of the dog with increase in the degree of gastric distension supine Bars indicate standard error

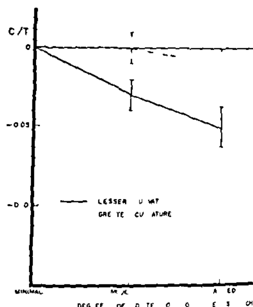


Fig 6 Fall in temperature (°C) in human gastric mucosa with increase in the degree of gastric distension with air supine Bars indicate standard error

of moderate, marked and extreme degrees of distension were 0.12° C ± 0.049° C ($P<0.05$), 0.19° C ± 0.054° C ($P<0.01$) and 0.33° C ± 0.042° C ($P<0.001$), respectively, while in the supine position they were 0.11° C ± 0.037° C ($P<0.05$), 0.22° C ± 0.062° C ($P<0.01$) and 0.33° C ± 0.053° C ($P<0.001$), respectively, (Table 2) These data suggest that the changes in temperature of the gastric mucosa do not alter with changes in the positions of the subject The same is true at the greater curvature The fall in mean temperature in the left lateral position when the stomach was inflated to the moderate, marked and extreme degrees were 0.02° C ± 0.029° C ($P<0.6$) 0.05° C ± 0.029° C ($P<0.2$) and 0.13° C ± 0.036° C ($P<0.02$) respectively, while in the supine position the mean temperature rose by 0.01 C ± 0.008° C ($P<0.3$) when the stomach was inflated to the moderate degree and fell by 0.01° C ± 0.022° C ($P<0.7$) and 0.10° C ± 0.028° C ($P<0.01$) respectively when the stomach was inflated to the marked and extreme degrees

Temperature of the gastric mucosa examined in the right lateral position The fall in mean temperature at the lesser curvature in the right lateral position at moderate, marked and extreme gastric distension were 0.04 C ± 0.034° C ($P<0.3$), 0.17° C ± 0.069° C ($P<0.05$) and 0.27° C ± 0.077 C ($P<0.02$) respectively, while in the supine position the mean temperature rose by

subject the temperature fall at a marked degree of gastric distension compared with a minimal degree of gastric distension was 0 05° C (P<0 001)

The fall in temperature in this experiment may indicate the decrease of blood flow, although because there is no way of recording the actual temperature gradient between the temperatures of the gastric wall and the core body, the exact amount cannot be determined quantitatively The present method may not be exactly a quantitative one but is a practical and reliable means of estimating the blood flow change Furthermore the thermistor used in this experiment has the advantage of high sensitivity to temperature by its instant reaction and the high temperature coefficient of the electric resistance

Certain observations on the morphology of the empty although not distended stomach (1 2 3 4, 5 6 10) should be mentioned BARLET (1924) and COLE (1929) reported that the arteries of the lesser curvature of the human stomach are much more sparse than those of the remainder of the stomach and are predisposed to occlusion REEVES (1920) reported that the submucosal arterioles at the lesser curvature are not only remarkably thinner and longer but also lie without anastomoses near the mucosal layer thus a greater resistance to the blood flow in this region results in a decreased blood flow and consequent risk of thrombosis DORAN (1951) suggested however that in the normal stomach and in cases of duodenal ulcer no significant difference in the vascular density between the lesser curvature and other parts existed and KEY (1950) stated that the vessels of the mucosa of the lesser curvature of the normal stomach are profuse and complex According to BENTLEY et coll (1951) there is no difference in the vascular density between the lesser curvature mucosa and that lining the rest of the stomach

In view of the possibility that blood stasis in the dependent portion of the stomach due to gravity may influence the local temperature the change in the mucosal temperature of the greater and lesser curvatures of the stomach when the examinee was changed from the supine to the right and left lateral positions were studied The result indicated that there was no significant difference in temperature as the position of the body was changed

The fall in temperature of the gastric mucosa when the stomach is distended beyond a certain degree may be attributed to local ischemia due to decrease in the local blood flow This local ischemia might cause a derangement of the normal function and a decrease in tissue resistance in that area and subsequently might predispose that area to certain disease such as carcinoma From this viewpoint the reports of ORR (1935) PEACOCK (1943) and TANNENBAUM (1954) are of interest

ORR (1935) stated that the induction of tumours of the skin in mice by local tar was appreciably accelerated by procedures interfering with the normal

Table 4

Degree of distension (increase) in human subjects supine position recorded in relation to the fall in temperature C, in the gastric mucosa — P indicates the significance level when compared with the temperature at minimal distension

Site	Lesser curvature*		Greater curvature**	
Degree of distension	Moderate	Marked	Moderate	Marked
Mean	0.03	0.0[illegible]	0.00	0.01
Standard error	0.009	0.012	0.009	0.011
P <	0.01	0.001		0.4

* 34 observations
**22 observations

Discussion

The incidence of gastric carcinoma in the Japanese has been reported to be higher among big eaters and lower among small eaters (11), as previously stated KIM & JAKOBSSON (1962) performed an experiment in rats to investigate changes of blood flow as the stomach is distended and found a considerable decrease in blood flow in the gastric antrum, especially at the lesser curvature when the stomach was distended beyond a certain degree. They suggested that this might contribute at least in part to the development of carcinoma and other gastric diseases that prevail in the antrum and at the lesser curvature of the stomach. Their method was not however applicable to human subjects.

The present authors developed a thermistor device that could measure precisely a minute variation in temperature and thus register changes in the temperature of the gastric mucosa in human subjects and dogs in vivo. This change in temperature, as will be discussed later, reflects the changes in blood flow of the stomach in various degrees of distension.

The mucosal temperature of the stomach, i.e. the blood flow of the stomach, in the experiment in the dog dropped significantly as the stomach was distended with air, the temperature fall becoming greater as the distension of the stomach was increased, the rate of fall was more marked at the lesser than at the greater curvature. This phenomenon was also observed, although to a lesser degree in the human stomach and was similar to that observed by KIM & JAKOBSSON in the rat stomach. The temperature fall in the dog, at marked and extreme degrees of gastric distension compared with a minimal degree of gastric distension, were 0.17° C ($P<0.001$) and 0.29 C ($P<0.001$), and in the human

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vascular supply. PEACOCK suggested that tissue of normal resistance does not react to a carcinogen unless its equilibrium is in some way disturbed. TANNENBAUM (1954) reported that in animals fed on restricted diets the tumour incidence is strikingly decreased, and the time at which neoplasms appear is delayed. He also pointed out that statistical evidence indicates a similar factor in man, as individuals who are overweight are more likely to die of carcinoma. (General restriction in diet should be clearly distinguished from deficiency diets which may give rise to conditions predisposing to carcinoma.)

The fact that the results of the experiments of ARVBEHETY et coll. (1959), DEMLING & WACHSMANN (1961), and others who studied the blood flow of the stomach morphologically or quantitatively, are not in keeping with the present authors' work seems to be due to the circumstance that the experiments of the former were performed in empty state, i. e. in the fasting of the morbid stomach.

Acknowledgements

The authors would like to acknowledge their indebtedness to the late Professor S. Hultberg for the help given. They are also much indebted to the Stockholm Cancer Society for financial support.

SUMMARY

The difference in temperature of the gastric mucosa between minimal and other degrees of distension were compared in dogs and human subjects by means of a sensitive intragastric thermistor. Distension of the stomach beyond a certain degree appeared to produce a marked fall in the temperature of the mucosa of the lesser curvature as compared with the greater. The significance of this in the etiology of pathologic conditions such as carcinoma in human subjects is discussed.

ZUSAMMENFASSUNG

Mit Hilfe eines hochstempfindlichen Thermistor-Thermometer wurde die Temperatur der Magenschleimhaut an Menschen und Hunden bei verschiedenen Ausdehnungsgraden des Magens gemessen. Bei grösserer Magenausdehnung zeigte sich ein stärkerer Temperaturfall an der kleinen Kurvatur als an der grossen Kurvatur. Die Bedeutung dieses Befundes für die Entstehung von Magenerkrankungen wie z. B. des Karzinomes wird erörtert.

RÉSUMÉ

Les différences de température de la muqueuse gastrique suivant que l'estomac est plus ou moins distendu ont été comparées chez l'homme et chez le chien grâce à un « thermistor thermomètre » intragastrique sensible. La distension de l'estomac au delà d'un certain degré paraît entraîner un abaissement marqué de la température de la muqueuse de la petite courbure par rapport à la grande courbure. Les auteurs étudient l'importance de ce fait dans l'étiologie de certaines maladies telles que le cancer chez l'homme.

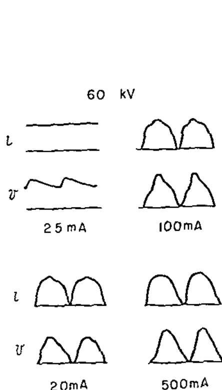


Fig 1 Typical applied voltage waveforms of a single phase unit

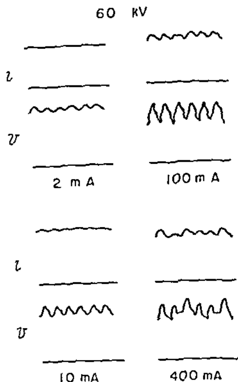


Fig 2 Typical applied voltage waveforms of a three phase unit

Applied voltage and tube current waveforms Applied voltage and tube current waveforms from single phase or three phase roentgen units are not simple rectified sine waves but vary in complexity with kilovoltage and milliamperage Typical waveforms are reproduced in Figs 1 and 2 It will be seen that the sine wave is distorted and that parasitic oscillations sometimes appear These two phenomena have been theoretically reduced from the saturating properties of tube current to tube voltage and from the electric circuit elements of the units (KANAMORI 1965)

If the milliamperage is low the applied voltage pulsation is decreased by the condenser effect of the cables between the high voltage generator and the roentgen tube

Fig 3 depicts tube current waveforms as well as applied voltage waveforms with a low kilovoltage of a single phase unit With high milliamperage the tube current saturation is low or negligible at the applied voltage so that the

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by

HITOSHI KANAMORI

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This paper deals with waveforms produced by a single phase and a three phase unit, their effects on the properties of the radiation and therefore the roentgenograms, and a comparison is made between two types of units regarding exposure factors in roentgenography This kind of investigation is possible since accurately applied voltage peaks as well *as waveforms may be obtained* by theoretical and experimental means (KANAMORI 1965) Accurate kilo voltage is desirable since a small error results in a large deviation in the quantity of radiation

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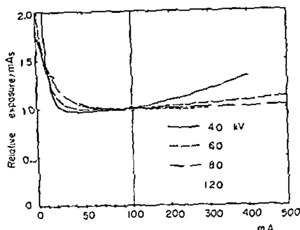


Fig 4 Relation between relative exposure and mA of a single phase unit at various kilovoltages At low mA the exposure/mAs increases due to a decrease in applied voltage pulsations With large mA of low kilovoltage curves exposure/mAs increases due to an increase in the mA peak/mA mean

attached to the chambers i e the effective kilovoltage was obtained from aluminium half value layers and by correcting repeatedly the absorption curves measured The focus chamber distance was 180 cm

The field size was 1 5 × 1 5 cm² (with screen), or 5 5 × 13 cm² (with ionization chamber) with the phantom centered between the focus and the chamber (or the screen) with a lead diaphragm and shutter to remove secondary radiation Phantoms in place of objects were located at the mid point between the focus and chamber to minimize the effects of secondary radiation (TROUT et coll 1960) Aluminium and acrylite sheets were used for the phantoms

The effects of change in milliamperage under the same kilovoltage and mAs settings were first checked The relative exposure due to rays transmitted through the 10 cm acrylite phantom was measured at various kilovoltages with an ordinary intensifying screen Shimadzu FD its fluorescence brightness being calculated by means of intergrating the photo current in a photo multiplier 931A The results with a single phase and a three phase unit respectively in which brightness per milliampere for each kilovolt was put at unity at 100 mA and 300 mA respectively are shown in Figs 4 and 5 Since the change in radiation quality is negligible at the same kilovoltage screen brightness is proportional to the exposure per unit mAs in each curve the ordinates in the figures therefore represent the relative exposure/mAs

It will be seen from these diagrams that

1 The exposure/mAs increases when a low milliamperage is used an increase that may be caused by a decrease in the voltage pulsations

2 With a high milhamperage and a low kilovoltage in a single phase unit

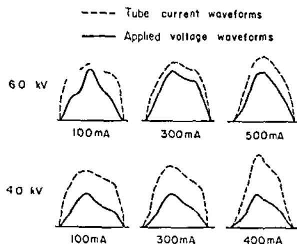


Fig 3 Applied voltage waveforms and tube current waveforms of a single phase unit at low kilovoltages At higher mA current saturation is small or negligible due to tube property The current waveform is therefore steep at the top and current peak current mean ratios increase more than otherwise

peak of the current waveform is steep and forms a triangle similar to that of the voltage waveform The current saturation in other cases increases as the voltage increases so that the peaks of the current waveforms become flatter than those of the voltage waveforms Areas under the current waveforms were made identical for each kilovoltage in Fig 3 so that the ratios of the current peak (mA peak) to current mean values, i e milliamperages (mA) could be compared by measuring the peak heights It is evident that the ratio of mA peak to mA becomes larger especially with unsaturated tube currents, i e at lower kilo voltages and higher milliamperages As, however, the current and voltage pulsations with a three phase unit are less than those with a single phase unit the mA peak/mA ratio is little affected by current saturation

Experiments on emission and transmission A roentgen tube was connected to an ordinary single phase and a typical three phase unit alternately in order to compare the effects of different units without changing the geometrical factors Katsura 150 III (150 kV, 500mA), Heian II (125 kV, 1 000 mA), and Circlex 2 (rotary anode tube, 2 mm focus), all manufactured by Shimadzu Seisakusho Ltd, were the respective single phase and three phase units, and the tube employed The waveforms in Figs 1 and 2 were measured with these units The peak voltage applied to the tube was measured by means of a sphere gap and an oscilloscope, the results obtained were the same as those calculated from basic electric circuit theory (KANAMORI 1965) The exposure in air was measured by a Victoreen's Radocon with a No 613 probe, or a Con denser-R-Meter with a No 130 probe The readings must be calibrated when the effective kilovoltage of radiation is less than 35 This calibration was com pleted by means of the data of calibration coefficients to the effective kilovoltage,

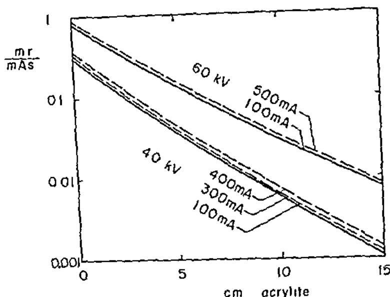


Fig 6 Measured exposure due to transmitted rays as a function of tube current The exposure is proportional to mA peak/mA mean

It would thus appear evident that the exposure due to rays transmitted through objects depends upon the applied voltage peak values (kilovoltage) applied voltage pulsation rates and tube current peak values but not on mean values (milliamperage) Waveform distortion from a sine wave and parasitic oscillations are without practical effects

Emission and transmission produced by constant potential, single phase and three hase waveforms It is clear from the conclusion of the preceding section that the exposure produced by emitted and transmitted rays may be calculated if the calibration for mA peak effects are added to the data of various kilovoltage (kV) and applied voltage pulsation rates Experiments on the emission and transmission of radiation were therefore performed Data on single and three phase waveforms were obtained from the two units used before Capacitors were also connected to the three phase unit for producing constant waveforms and amplifying the smoothing effects of the cable capacitors The value of milliamperage for each kilovoltage was so selected that the applied voltage pulsation rates in the three kinds of waveforms were 1 0 3 and 0 respectively At low kilovoltage with the single phase unit data on current saturation were used

Figs 7 and 8 show the exposure in air thus obtained from the three kinds

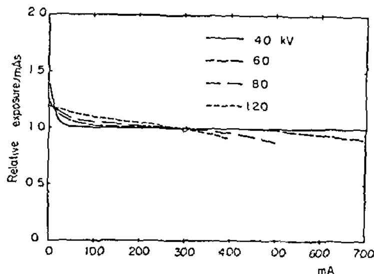


Fig 5 Relation between relative exposure and milliamperage of a three phase unit at various kilovoltages Exposure/mAs decreases as mA increases due to increase in applied voltage pulsation rates

i e when the tube current produces little, if any, saturation, the exposure/mAs increases directly with the milliamperage (Fig 4), this may be caused by the effect of increasing the mA peak value

3 The exposure/mAs of a single phase unit does not change in other conditions than the above mentioned but the applied voltage falls to zero every half cycle and the tube current saturates

4 With a three phase unit the exposure/mAs decreases with increase in milliamperage since the applied voltage pulsation rate increases directly with increasing milliamperage

The second factor was examined in detail The exposures due to emitted and transmitted rays for various milliamperages were measured and plotted as shown in Fig 6 Values under 1 mA are not included as the figure is not meant to indicate constant voltages (See solid lines in Figs 7 and 8 in which constant voltages under 1 mA are indicated) It is apparent that with a low kilovoltage of the single phase unit, the exposure/mAs increases directly with milliamperage This change is evident at 10 kV, whereas little change occurs at 60 kV The exposure/mAs is almost proportional to the ratio of mA peak/mA over the entire thickness range, where the ratio is measured from the peak heights of the broken line waveform curves in Fig 3 The reason for this may be that even if the applied voltage and current waveforms change the property of the radiation when the kilovoltage is low, say between 40 and 60 kV, soft ray components may be absorbed by primary filter and object, so that only the hardest rays generated at peak voltage are transmitted Current and voltage reach their peak values together Consequently, with a low kilovoltage the exposure due to the transmitted radiation may be proportional to the mA peak value even if only the primary filter transmission is measured

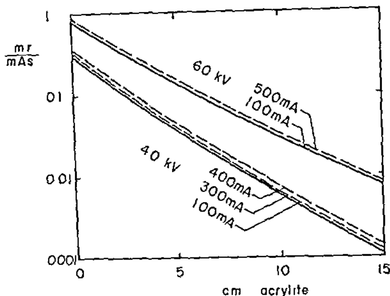


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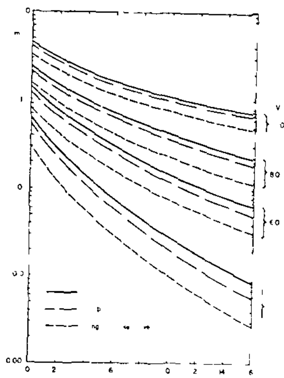


Fig 7 Measured exposure due to transmitted rays through aluminium phantom for constant potential three phase and single phase waveforms

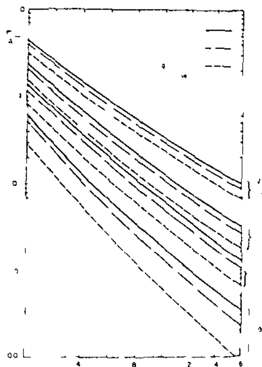


Fig 8 Measured exposure due to transmitted rays through acrylite phantom for constant potential three phase and single phase waveforms

of waveforms with aluminium and acrylite phantoms The ordinates are logarithmic exposure/mAs The figures facilitate investigation of the radiographic effects, as discussed later, and the following facts may be noted

1 At the same kilovoltage, constant waveforms generate a harder quality and a larger quantity of radiation than single phase waveforms This is well known but does not seem to have been accurately measured before

2 With 40 kV the first and the second half value layers of aluminium from a constant waveform are 1 52 and 1 78 mm, and those from a single phase waveform 1 45 and 1 66 mm, respectively The difference in hardness, however, decreases with increase in kilovoltage and disappears when the kilovoltage exceeds 80 This is true also when acrylite phantoms are used

3 The ratio of exposure from a constant waveform to that from a single phase waveform increases with decreasing kilovoltage and increases with increase in object thickness The ratio with 40 kV through 10 cm acrylite is 3 16, while with 60, 80, and 120 kV the ratios decrease to 2 14 2 00, and 1 77, respectively

The above properties are dependent on the soft radiation absorption rates

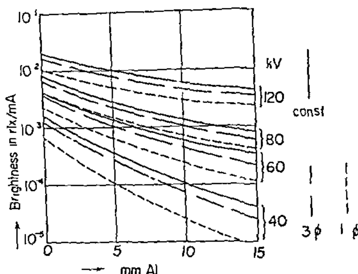


Fig 9 Screen brightness generated by transmitted rays through aluminium phantom

of the objects The radiation produced by a single phase waveform is softer than that of a constant potential waveform radiation This difference is particularly apparent as the kilovoltage decreases

4 The transmitted radiation becomes harder as the thickness of the object increases This is more marked with aluminium than with acrylite absorption coefficient characteristics of acrylite are more constant than those of aluminium so that soft radiation is absorbed more rapidly by the latter than by acrylite

Effects of screen brightness Screen brightness due to transmitted radiation should be measured in any consideration of optimum exposure factors in radiography An ordinary screen *Shimadzu FD was used in the present* investigation The brightness was detected with a photomultiplier 931A and calibrated into radlux (≡ blondel) with a lux meter which is sensitive only to visible rays The screen emits a large amount of ultra violet radiation which influences the 931A to the same degree as it does a roentgen film The spectrum of emitted rays of a screen is however almost independent of the quality of the incident rays and the brightness in radlux is therefore a relative value of screen brightness effectively absorbed by the film emulsion

The results of aluminium and acrylite phantoms respectively, are plotted in Figs 9 and 10 which show the same properties as the exposure/mAs data of Figs 7 and 8 although the bends of the brightness curves at low kilovoltage

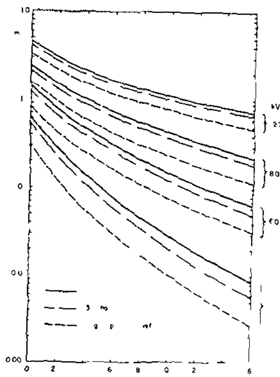


Fig 7 Measured exposure due to transmitted rays through aluminium phantom for constant potential three phase and single phase wave forms

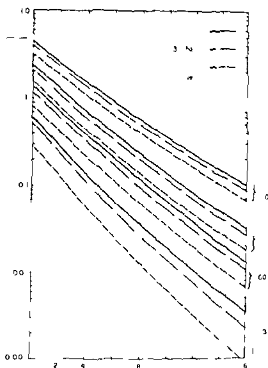


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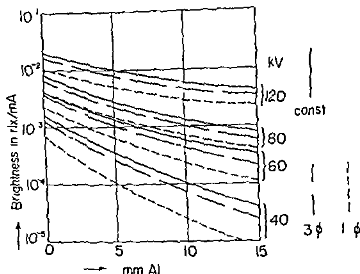


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Effects of screen brightness Screen brightness due to transmitted radiation should be measured in any consideration of optimum exposure factors in radiography An ordinary screen Shimadzu FD was used in the present investigation The brightness was detected with a photomultiplier 931A and calibrated into radlux (≅ blondel) with a lux meter which is sensitive *only to visible rays The screen emits a large amount of ultra violet radiation* which influences the 931A to the same degree as it does a roentgen film The spectrum of emitted rays of a screen is however almost independent of the quality of the incident rays and the brightness in radlux is therefore a relative value of screen brightness *effectively absorbed by the film emulsion*

The results of aluminium and acrylite phantoms respectively are plotted in Figs 9 and 10 which show the same properties as the exposure/mAs data of Figs 7 and 8 *although the* bends of the brightness curves at low kilovoltage

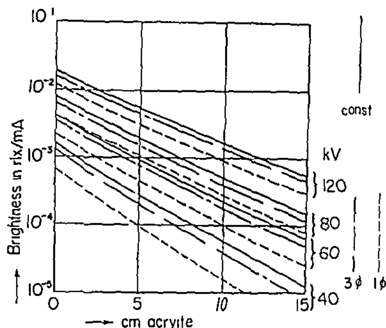


Fig 10 Screen brightness generated by transmitted rays through acrylite phantom

are less than those of the intensity curves, due to the fact that the light emission efficiency of a screen increases with the hardness of the incident rays

The light emission efficiency of the screen obtained from Figs 7 and 9 and from Figs 8 and 10 are shown in Fig 11 As this diagram indicates, the efficiency is a function of the quality of incident rays but independent of applied voltage waveforms, a simple relationship between screen brightness and exposure due to incident rays may be expressed

38 8 × 10^{-3} × k × exposure in mR = screen brightness in radlux second, where, k is the relative efficiency is a function of HVL or effective kilovoltage when an efficiency with 9 mm Al HVL is unity, this k is shown in Fig 11

Optimum exposure factors in roentgenography The composition and thickness of the object in diagnosis are generally complex, and any changes should be perceptible both at the low and high density areas of a roentgenogram Wide ranges of density and thickness are consequently important The author stated in a previous paper (KANAMORI 1966) that an optimum density range could be found for each combination of objects and inspecting factors, and that the optimum exposure factors of kilovoltage and mAs were such that the density produced by the object thickness range under examination just covered this density range

Fig 12 illustrates the means for obtaining the optimum factors The abscissa

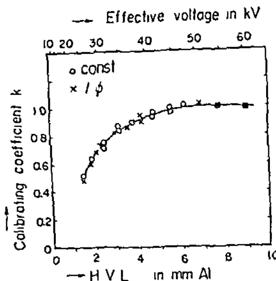


Fig 11 Calibrating coefficient k for the calculation of the efficiencies of an intensifying screen type Shimadzu FD Screen brightness depends only on effective kilovoltage

$(x_1\ x_2)$ is the object thickness range under examination, and the ordinate represents the logarithmic screen brightness range ($\log E_1$ $\log E_2$) corresponding to the optimum density range of the film emulsion to be used The curve representing the optimum factors passes through the two corners of the rectangle If the kilovoltage or mAs do not correspond to the optimum, however, the abscissa or/and the ordinate are not used entirely The contrast ΔD constituted from change in thickness Δx increases with the change in logarithmic brightness Δ ($\log E$) and Δ ($\log E$) increase with the gradient of the absorption curves The film contrast in the optimum case is therefore the *greatest and without deficiency over the entire thickness range*

The optimum factors may therefore be obtained from thickness to logarithmic screen brightness curves such as those of Fig 9 or 10 as follows the rectangle in Fig 12 is displaced along the ordinate of Fig 9 or 10 so that the thickness range (x_1, x_2) of both figures coincide and the curve passing through the two corners of the rectangle is found The optimum kilovoltage is then the *parameter of the curve and the optimum mAs with 180 cm FFD is obtained* as E_1/a where a is the reading of the ordinate of Fig 9 or 10 at the corner (x_1 E_1) of the rectangle of Fig 12 If FFD is not 180 cm the inverse square law should be applied for the mAs data calibration for the milliampere peak effect should also be performed

The optimum factors of the three waveforms obtained by utilizing the above procedures were plotted as in Fig 13, where for example the range of the

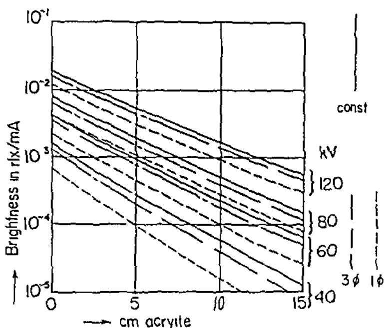


Fig 10 Screen brightness generated by transmitted rays through acrylite phantom

are less than those of the intensity curves, due to the fact that the light emission efficiency of a screen increases with the hardness of the incident rays

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$38.8 \cdot 10^{-4} \cdot k \cdot$ exposure in mR = screen brightness in radlux second, where, k is the relative efficiency as a function of HVL or effective kilovoltage when an efficiency with 9 mm Al HVL is unity, this k is shown in Fig 11

Optimum exposure factors in roentgenography The composition and thickness of the object in diagnosis are generally complex, and any changes should be perceptible both at the low and high density areas of a roentgenogram Wide ranges of density and thickness are consequently important The author stated in a previous paper (KANAMORI 1966) that an optimum density range could be found for each combination of objects and inspecting factors, and that the optimum exposure factors of kilovoltage and mAs were such that the density produced by the object thickness range under examination just covered this density range

Fig 12 illustrates the means for obtaining the optimum factors The abscissa

Range of thickness	0-X	X/3-X	X/2-X
Curve	A	B	C

X Thickness of object

—— const
— — 3 ϕ
- - - - 1 ϕ

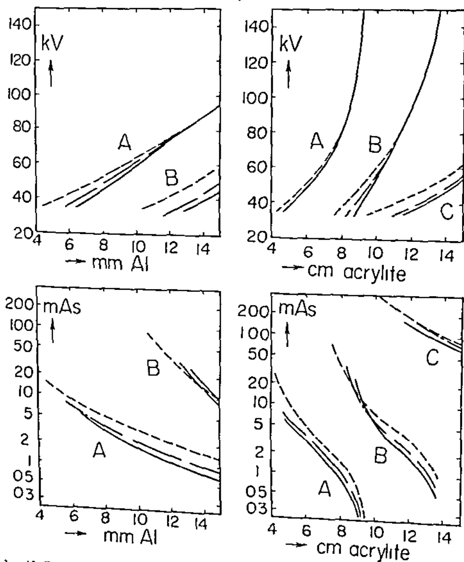


Fig 13 Optimum kilovoltage and mAs of aluminium and acrylite phantoms

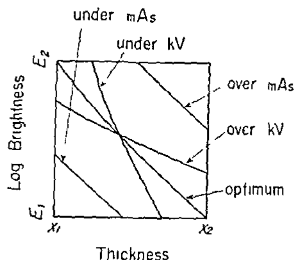


Fig 12 Methods of obtaining optimum exposure factors kV and mAs in roentgenography

ordinate of the rectangle is given (log 0 7 10^{-3}, log 6 0 10^{-3}) This exposure range is of a typical emulsion, FUJI PX, and corresponds to the optimum density range (0 27, 1 75) of chest roentgenograms under ordinary viewing factors (KANAMORI 1966) Curves A, B, and C in the figure correspond to the thickness range under examination Curve A yields data when zero to maximum object thickness X is tested, whereas B and C provide data when only over a half and one third, respectively, of the maximum thickness are tested It follows that

1 Optimum kilovoltage and mAs increase with increase in object thickness

2 With the exception of the thin parts of an object, as the thickness range decreases, optimum kilovoltage decreases and contrast increases, whereas mAs must be increased in order to obtain optimum density

3 Optimum kilovoltage and mAs increase with increase in the applied voltage pulsation for the same object The difference between a constant potential and a single phase waveform is greater than 10 kV at a low kilovoltage, decreases with increase in kilovoltage and becomes zero when the optimum kilovoltage exceeds 80 The ratio of the optimum mAs sometimes exceeds 2 This suggests that the sharpness of a roentgenogram with a single phase unit is poorer than with a three phase unit because the former demands a longer exposure time

The relationship of waveforms to the properties of roentgen rays and optimum factors of kilovoltage and mAs have thus been considered The primary filter, roentgen ray production efficiency, intensifying screen, optimum density range, and object may be different from those in the present investigation, but if the same procedures as those described are used the effects upon the waveforms may be calculated and recorded

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TANDERIL® IN THE TREATMENT OF RADIATION CYSTITIS

by

STEEN JOHANNESSEN

Radiotherapy of malignant vesical tumours may cause the development of radiation cystitis This may in turn produce severe bladder tenesmus and often later lead to chronic cystitis with thickening of the bladder wall and reduced bladder capacity Severe tenesmus may necessitate large doses of narcotics and initiate drug addiction Secondary chronic radiation cystitis with much reduced bladder capacity causes the patient a great deal of inconvenience

Excellent antiphlogistic effects have been obtained with p hydroxyphenyl butazone (Tanderil®, Geigy) a metabolite of phenylbutazone (Butazolidin®) in other cases of postoperative oedema and inflammation as for instance after the surgical treatment of varices phimosis and haemorrhoids Tanderil was therefore administered as an adjunct to the treatment of vesical tumours with radioactive tantalum (^{182}Ta) Even though the material comprises only ten patients with malignant bladder tumours treated in the department for a year the uniform results may justify this report A paper by ERWIN K SCHMIDT (1962) who mentioned the favourable effect of Tanderil in telecobalt therapy

From the surgical Department (Director Erik Henrichsen) Centralsygehuset Slagelse Denmark Submitted for publication 22 March 1965

SUMMARY

Applied voltage and tube current waveforms produced by single or three-phase roentgen units are not simple rectified sine waves but vary with kilovoltage and milliamperage Transmitted roentgen ray properties may however be determined from the applied voltage pulsation, mA peak, and applied voltage peak A new definition of optimum exposure factors (kV and mAs) in roentgenography is given Brightness of an intensifying screen depends upon effective kilovoltage of the incident rays and not upon waveforms

ZUSAMMENFASSUNG

Die Rohrenspannung und die Stromwellenform von ein oder dreiphasigen Transformatoren sind nicht einfache Sinuswellen sondern sie schwanken je nach den Kilovolts oder den Milliampères Die Strahlenqualitat kann jedoch entspechend der verwendeten Voltpulsierung der Spitzen mA und der Spitzenspannung bestimmt werden Eine neue Definition der optimalen Belichtungsfaktoren (kV und mAs) wird angegeben Die Helligkeit der Verstarkungsfolien beruht auf den effektiven Kilovolts der Einfallsstrahlung und nicht auf der Wellenform

RÉSUMÉ

Les courbes représentatives de la tension et de l intensité du courant fourni au tube par les générateurs mono ou triphasés ne sont pas de simples sinusoides redressées mais varient suivant la tension et l intensité On peut cependant déterminer les propriétés du rayonnement roentgen émis d après la pulsation de la tension appliquée au tube le maximum de l intensité et de tension L auteur donne une nouvelle définition des facteurs d exposition (kV et mAs) optimaux en radiographie La brillance d un écran renforçateur dépend de la tension efficace des rayons indicents et non de la forme de l onde de tension

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therapeutically active concentration on the day of operation, an administration of Tanderil suppositories 250 mg × 3, and, postoperatively Tanderil tablets 100 mg × 3 daily as a maintenance dose for average of 10 7 days

Results were assessed on the patients symptoms in the post operative period as well as their bladder capacity at routine control cystoscopies performed every third month

In order to observe the effect of Tanderil alone the vitamin prophylaxis advised by some authors (HELLRIEGEL 1962 SCHMIDT 1962) was omitted Another possible measure was to reduce radiation intensity to the rest of the mucosa by using an 18/30 instead of an 18/5 Foley catheter so as to keep the bladder more distended during tantalum treatment and thereby increase the distance from the tantalum needle to mucosa not requiring therapy, however, this was not done so as to leave conditions uniform during the evaluation of Tanderil

Results

The first three patients received a loading dose of 200 mg Tanderil on the evening of the operation day followed by 200 mg × 3 daily until a total of 1 200 mg had been given and then 100 mg × 3 daily One of these patients (Case 2) had mild vesical tenesmus the day after operation this passed off in the course of the day however without the administration of analgetics and did not recur during the rest of his stay in hospital The tenesmus in this patient may be explained by the fact that two tantalum needles had been applied and that a sufficient concentration of Tanderil had not been obtained by the time this is why in later patients (Cases 4 to 10) a loading dose was administered 2 days before surgery The last four patients were given suppositories None of these 7 patients had tenesmus in the postoperative period during which they received Tanderil In one patient (Case 7) tenesmus occurred the day after withdrawal of the preparation a new loading dose was therefore given for two days followed by a maintenance dose for another two days after which the patient remained free of symptoms for the rest of his stay in hospital Thus 8 patients were entirely free of tenesmus

Only one patient (Case 5) had seriously reduced bladder capacity (from 250 ml to 75 ml at follow up 4 months after surgery) but by mistake this patient was given only 200 mg Tanderil three times a day for three days and nothing on the day of operation No maintenance dose was thus administered during the rest of the postoperative period and from the 14th day the patient suffered from pollakiuria dysuria and urgency of micturition complications subsiding after the administration of Skopyl® 1 t d s The reduced bladder

Table

Total Tanderil dosage, postoperative tenesmus and bladder capacity at last control cystoscopy

No	Total dose in mg	Tenesmus	Bladder capacity in ml
1	1800	None	100
2	1500	None (except 1st day)	300
3	1200	None	200
4	1800	None	300
5	2000	None	75
6	1500	None	350
7	5850	None (except 11th day)	Has not reported for control
8	4950	None	Died before control
9	5850	None	300
10	6450	None	200

of bladder tumours, appears to be the only previous reference to this form of treatment.

A dosage of 6 000 R at the site of the tumour should be the aim in radio therapy of vesical tumours. Since radiation intensity decreases with the square of the distance, the remainder of the mucous membrane will also be exposed to a not insignificant though smaller dose and may become affected.

Briefly, our technique (CHRISTOFFERSEN 1958/1959) has been as follows. The tumour and surrounding mucosa are excised through a cystotomy incision down to the vesical musculature, the resection surface is then electrocoagulated and the mucous membrane closed over this surface with continuous nontraumatic chromic catgut. One or more tantalum needles, depending on the extent of the resected area, are applied to the mucous membrane along the suture line. The needle is fixed with a nylon suture to a Foley catheter inserted through the urethra, and the bulb of the catheter is filled with 5 ml of water. The optimal radiation effect lies within a range up to 0.5 cm (CAMPBELL 1963), so that a considerable local radiation effect is obtained for from 18 to 144 hours, depending on the size of the area and the actual radiation intensity of ^{182}Ta on the day of operation.

The ten cases reported include all patients who during the period under review had vesical tumours treated with radioactive tantalum.

The Tanderil dosage varied a little at the beginning as regards time of onset and treatment on the day of operation but when Tanderil suppositories became available for the last 4 patients the following doses were given: Tanderil tablets, 200 mg three times a day for two days prior to surgery to obtain a

therapeutically active concentration, on the day of operation, an administration of Tanderil suppositories 250 mg × 3 and postoperatively Tanderil tablets 100 mg × 3 daily as a maintenance dose for average of 10 7 days

Results were assessed on the patients symptoms in the post operative period as well as their bladder capacity at routine control cystoscopies performed every third month

In order to observe the effect of Tanderil alone the vitamin prophylaxis advised by some authors (HELLRIEGEL 1962 SCHMIDT 1962) was omitted Another possible measure was to reduce radiation intensity to the rest of the mucosa by using an 18/30 instead of an 18/5 Foley catheter so as to keep the bladder more distended during tantalum treatment and thereby increase the distance from the tantalum needle to mucosa not requiring therapy however this was not done so as to leave conditions uniform during the evaluation of Tanderil

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capacity in this patient should be attributed to insufficient Tanderil dosage during the postoperative period

Two patients (Cases 3 and 10) have slightly reduced and 5 have normal bladder capacity One patient (Case 7) has not reported for follow up examination despite repeated requests although it is reported that he is perfectly well One patient (Case 8) died before the first follow up cystoscopy

No untoward effects were noted in any of the patients

It has not been possible to decide whether Tanderil had any protective effect on the tumour cells No evidence of delayed wound healing (FRIDRICH 1963, SCHMIDT 1962) has been apparent

Discussion

The results obtained are given below

	Excellent	Good	Poor
Prevention of tenesmus	8	2	0
Bladder capacity	5	2	1

The results achieved are striking and seem satisfactory in the prevention of chronic cystitis, in comparison with the discomfort due to radiation cystitis in patients untreated by Tanderil

Tanderil will continue to be indicated even though the radioactive tantalum treatment of malignant vesical tumours may be superseded by ^{60}Co teletherapy (SCHMIDT)

The toxicity of Tanderil is reported by several authors to be low The effect on the gastric mucosa is stated to be less than that of Butazolidin and the risk of agranulocytosis small Two cases of agranulocytosis occurring during Tanderil treatment have been reported in Denmark (JOHANSEN 1962, TOJNER 1963) but the haematologic appearances quickly returned to normal after the withdrawal of the preparation and simultaneous institution of steroid therapy

The only absolute contraindications to Tanderil are stated to be gastric and duodenal ulceration Relative contraindications are the presence of cardiac, renal or hepatic insufficiency (HUSTED & HJORTING HANSEN 1962 SCHMIDT 1962)

SUMMARY

Ten patients were given Tanderil to prevent discomfort due to radiation cystitis produced by radioactive ^{182}Ta treatment of malignant tumours of the urinary bladder The results achieved were excellent as regards tenesmus and satisfactory as to bladder capacity since only one patient had a significant reduction Tanderil probably deserves a trial in ^{60}Co teletherapy of vesical tumours

ZUSAMMENFASSUNG

Zur Milderung der Bestrahlungs Cystitis die nach der Behandlung von Blasentumoren mit radio-aktivem Ta aufzutreten pflegt wurde den Patienten Tanderil verabreicht Sehr gut Resultate wurden beim Tenesmus erzielt und die Blasenkapazitat war zufrieden stellerd nur ein Patient litt an stark verminderter Kapazitat Tanderil ist ein Mittel das es wohl verdient bei Telekobaltbestrahlung von Blasentumoren benutzt zu werden

RÉSUMÉ

Des malades traités par le Ta radioactif pour tumeur maligne de la vessie ont reçu du Tandéril pour prévenir les inconvénients de la radiocystite Les résultats ont été excellents en ce qui concerne le tenesme et satisfaisants pour la capacite vésicale qui n a subi une réduction importante que dans un cas Le Tanderil mérite probablement d etre essayé dans le traitement télécobalt thérapique des tumeurs vesicales

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FROM THE RHEUMATISM FOUNDATION HOSPITAL (DIRECTOR DOCENT V. LAINE), HEINOLA, FINLAND

GROWTH DISTURBANCE OF THE MANDIBLE IN JUVENILE RHEUMATOID ARTHRITIS

by

EERO SAIRANEN and EEVA HELMINEN PAKKALA

The detection of changes in the temporomandibular joint in juvenile rheumatoid arthritis presents both clinical and roentgenologic difficulties. Pantomography and orthopantomography (PAATERO 1953, 1954, 1959, TAMMISALO & MATTILA 1963, TAMMISALO 1964) seem in this respect to give better results than other roentgenologic methods, especially when the articular ends of the condyles are concerned.

Affection of the temporomandibular joint is common in adults (UOTILA 1964) but less frequent in children, in whom growth disturbance of the mandible, or micrognathia, occurs in 1 to 25 % of patients in different series (SAIRANEN 1964). Disturbance in growth of the mandible, following rheumatic arthritis of the temporomandibular joint, has been generally accepted as a cause of micrognathia (ENGEL et coll. 1949, CAFFEY 1961) though divergent opinions have been presented (DECOURT et coll. 1951, SAIRANEN).

Material and Methods. The material included 21 unselected patients suffering from rheumatoid arthritis that had commenced before the age of 15. Eight of the patients were boys. All the patients had been treated at the hospital and the diagnosis verified. The control group included 55 healthy children, who were all below 11 years of age.

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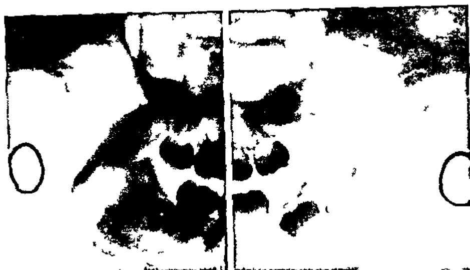


Fig 1 An apparently normal temporomandibular joint although clinically probably affected Disease of 2 years duration

The clinical examination comprised a recording of the history, and palpation of the temporomandibular joint for mobility and tenderness The condition was classified in four stages of severity (STEINBROCKER et coll 1949) The roentgenologic examination of the temporomandibular joint was carried



Fig Case 3 Considerable bilateral condylar flattening Slight abnormality of posterior margin of r us on left side

Table

Age at beginning of disease duration and degree of severity in patients with roentgen changes in the temporomandibular joint

Case	Age in years			Duration in years			Stages			
	<6	7—10	>10	2	3	>3	I	II	III	IV
3	+					+			+	
7	+					+				+
10			+	+					+	
3		+				+		+		
20	+				+		+			

out in the rheumatic subjects by orthopantomography, and on the control material by pantomography The rotational beams in the former turn successively about three axes so as to permit a penetration of the dental arches throughout their length, more or less perpendicularly, but the more dorsal areas in oblique projections The contours of the condyle will generally appear clearly, while the articular fossa may not be represented equally well

Results and Discussion

The temporomandibular joint was clinically proved to be affected in 3 patients of the rheumatic group Orthopantomography revealed changes in the condyle in 5 patients, in 2 of whom the temporomandibular joint was clinically affected Thus the joint was roentgenologically normal in one patient, in spite of the clinically indicated affection (Fig 1)

It may be mentioned that only one patient had had corticosteroid therapy for any considerable period (Case 10, see Table)

The temporomandibular joint, especially in the region of the condyle, proved to be normal in size and shape in pantomography of the jaw in the control group No essential difference could be noted between the dentition of the two groups

It is known that joint affections in children may be asymptomatic and this may well apply to the temporomandibular joint There is consequently not always any correlation between the clinical and roentgenologic findings Flattening or absence of the condylar head was apparent in the present material On the other hand, typical arthritic changes such as erosion or irregularity of the condylar surface, were evident only in 3 patients, in two of whom there was also a clinically proved affection of the joint The most marked



Fig 3 Case 7 Flattening of both condyles and marginal irregularities Micrognathia

changes appeared in a patient in whom the disease had run a course of only 2 years This patient had had corticosteroid therapy for a relatively long period FORSSLUND et coll (1961) described two adult subjects with absorption of the condyle and presumed the probable cause of this to be the prolonged exhibition of corticoids Corresponding cases may however be found in the present material in which corticoids were not used at all or only for short periods Arthritic changes in the temporomandibular joint obviously develop at inconstant rates

Considerable roentgen changes had occurred in the condyle in two patients of the present material before they were 6 years old and had lasted for 3 to 7 years Since mandibular growth reaches its maximum below the age of 6 years it might be supposed that micrognathia would have developed if affection of the temporomandibular joint is to be accepted as an exciting cause In the only patient with micrognathia in this material, changes in the condyle approximately corresponded to those in the other two patients It would thus appear that it is unlikely that temporomandibular joint affections alone are the cause of disturbances to the growth of the mandible

Acknowledgement

The author takes the opportunity of thanking the Terve lapsi Research Foundation for arranging for the control material

SUMMARY

Twenty four patients suffering from juvenile rheumatoid arthritis were submitted to orthopantomography of the jaw and 55 control patients were examined by pantomography It appears that disturbances to the growth of the mandible or micrognathia in children with rheumatoid arthritis may be produced by causes additional to affection of the temporomandibular joint

ZUSAMMENFASSUNG

Vierundzwanzig Patienten mit juveniler rheumatoider Arthritis wurden einer Orthopantomographie des Kiefers zugewiesen und 55 Kontrollpatienten wurden mittels Pantomographie untersucht Es scheint dass die Wachstumsstorungen des Unterkiefers — Mikrognathia — bei Kindern mit rheumatischer Arthritis durch Faktoren verursacht werden die zur Affektion des Kiefergelenkes noch hinzukommen

RÉSUMÉ

Vingt quatre malades atteints de polyarthrite chronique rhumatismale juvénile et 55 sujets témoins ont subi une orthopantomographie maxillaire Il en ressort que les troubles du développement de la mandibule ou la micrognathie peuvent chez les enfants atteints de polyarthrite chronique rhumatismale être dus à d autres causes que l atteinte rhumatismale de l articulation temporo maxillaire

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VARIATION IN RADIOSENSITIVITY OF MICE WITH TIME OF DAY

by

RICHARD F NELSON

For centuries there has been interest expressed in the variations of biological sensitivity with the time of day As early as 1797 HUFELAND of London published a monograph entitled *The Art of Prolonging Life* relating the 24 hour period and the regular revolution of our earth and how this affects the physical economy of man In 1938 JORES mentor of the Society for the Study of Biological Rhythms compiled a review of the voluminous literature on the physiology and the pathology of 24 hour rhythms In 1951 SMITH et coll of the United States Public Health Service reported on the effects of hibernation in the marmot on survival time following whole body radiation His numbers were small nine marmots in each group and he used two different doses delivering a higher dose to the hibernating animal than to the non hibernating animal His experiments showed that there was a delay in the occurrence of death following irradiation in the hibernating versus the non hibernating animal This phenomenon may be explained by the lower body temperature of the hibernating animal with an accompanying reduced metabolic rate The data

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indicates that there is no significant decrease in radiation lethality when the animal is in hibernation, and that reduced metabolic activity only produces a delay in the response and does not significantly alter the sensitivity

There have been several articles on the variation of sensitivity to ionizing radiation with age, one of the most extensive studies being that of STORER (1957, 1962) It has also been pointed out by EVANS et coll (1962, 1964) that there is an alteration in the radiosensitivity of mice using anesthesia RUGH et coll (1963) published data on a total of 2 347 mice of two different strains checking the survival time of the animals up to thirty days post radiation Whole body exposure was delivered to the mice using 184 kV roentgen rays with half value layer of 0 6 mm Cu In his study he was unable to obtain a statistically significant variation in the sensitivity STRAUBE (1963) exposed ninety female Sprague Dawley rats to 900 R using 280 kV roentgen rays with half value layer of 2 03 mm Cu to duplicate PIZARRELLO's (1961) experiment He was unable to confirm the dramatic results of the early paper of PIZARRELLO et coll (1963)

Although in the literature one does find such things as variation in sensitivity with temperature, age and anesthesia, there have been very few reports demonstrating the phenomenon of a diurnal variation in sensitivity until recently In 1963, we investigated this phenomenon in 468 mice Three different strains of female Jackson mice were used, C57BR, C57BL and CBA At that time, a significant difference in the radiation response as a function of the time of day was not demonstrated This may be explained in that the light dark cycle was controlled by manually turning the lights on and off five days a week, and also perhaps the estrus cycle caused us to show no significant variation in sensitivity

In August 1963, PILGRIM of Germany published a report, and, in 1963 also, PIZARRELLO presented data on forty rats which showed a variation in survival time after whole body radiation at two times of the day HALBERG (1959, 1963), particularly in his articles on the 24 hour cycle, showed that there was a variation following parenterally administered endotoxin In 1964, PIZARRELLO performed a new experiment to study the 24 hour cycle in mice to determine their variation in sensitivity to whole body radiation For ease in comparing results relative to irradiation time, PIZARRELLO put his data in terms of 'Arbitrary Zeitgeber Time (AZT), where 0000 equals 7 a m which is the beginning of the light cycle He was able to observe that the shortest survival time post radiation, occurred with the group irradiated at 2 a m local time or 1 900 AZT He also replotted RUGH's data in terms of days when 50 % of the population were dead as a function of the time of day, and he points out a remarkable coincidence of their two data

Table

Results obtained in the Swiss Webster mouse experiments

Group	\ZT	LD *	LD	TBW *	TBWd	TBWD / TBWT
1	0100	73 33	83 33	31 63	22 062	0 697
2	0300	73 33	80 00	31 11	?1 841	0 707
3	0500	76 67	90 00	30 57	20 711	0 688
4	0700	73 33	73 33	29 29	0 444	0 693
5	0900	0 00	90 00	29 84	19 356	0 649
6	1100	70 00	90 00	30 18	19 955	0 662
7	1300	83 33	96 67	29 91	18 778	0 618
8	1500	80 00	100 00	?9 43	19 400	0 660
9	1700	70 00	83 33	29 38	19 025	0 636
10	1900	86 67	100 00	30 34	18 994	0 617
11	2100	83 33	96 67	31 13	18 978	0 632
12	?300	70 00	96 67	30 57	19 325	0 655
Controls	—	—	—	29 14	29 746	1 027

* *Percent mice dead at fifteen and thirty days post radiation respectively*
Total body weights one day pre irradiation and at death respectively

Because of the indications both pro and con diurnal variations, a new study was undertaken to determine whether such *circadian* variations in susceptibility to radiation injury did exist

Method

In order to reduce the number of variables encountered in *trying to detect* diurnal variations the following steps were taken (1) each group within the series contained a *statistically significant* number of animals (2) the mice were all from the same breeder farm (3) the age range of the *mice* was ± 1 day (4) the mice were of the same weight ± 1 gram (5) the mice were acclimatized and conditioned *for a period of* at least 14 days prior to irradiation (6) only male mice were used to eliminate the possibility of the estrus cycle *overshadowing* any variation in diurnal sensitivity (7) the mice were irradiated during one 24 hour period

Four hundred male Swiss Webster mice 6 weeks old *were used in* our experiment The mice were placed in individual cages in a room with no other animals The weights of the *animals* were checked every 7 days The animals were divided into 13 groups the 12 radiation groups had 30 *mice* each and the *control* group had 40 The windows and the door in the animal room were covered so that no light could enter *the room* The lighting cycle was controlled

by an automatic clock and the lights remained on 7 days a week from 7 a m to 7 p m and off from 7 p m to 7 a m The mice were conditioned in this manner until they were 14 weeks of age or 8 weeks after they arrived at this institution On the 8th week plus 1 day, the 12 groups were irradiated The twelve groups were irradiated at 2 hour intervals For purpose of comparison, the times of irradiation relative to the day night cycle are expressed in terms of 'Arbitrary Zeitgeber Time' (AZT) Therefore the mice were exposed beginning at 0100 AZT, which was 8 a m

The animals were irradiated during a single 24 hour period so as to lessen the possibility of age and stock becoming another variable The animals were irradiated bilaterally using two Picker Vanguard 280 kV X ray machines operating at HVL 2 0 mm Cu with an exposure rate of 42 R/min A special jig was designed to hold thirty animals and to give a uniform dose to all animals Exposure was determined using a Victoreen electrometer with a chamber that had been calibrated at the National Bureau of Standards A check on the output was made after every third run during the experiment and it was found that the output did not vary more than ± 0 2 R/min For purposes of comparing our data with PIZZARELLO's, the 12 groups of mice were exposed to 800 R Commencing at 0100 AZT, the animals were brought to the roentgen room on racks, placed in the radiation holder and exposed The daytime group presented no problem at all However, the night group starting at 1300 AZT had to be kept always in the dark This was accomplished by having an opaque cover put over the animal rack when it was brought to and from the radiation room The animals were inserted into the radiation holder under essentially dark conditions except for a 15 watt dark red bulb

Starting with day-1 post radiation, the animals were checked twice a day for lethality At death, their total body-weight was determined The weights of the animals were not taken at any time post radiation except at death because of the possible added trauma which might alter the death rate

Statistical analysis

As can be seen from the Table, there appeared to be a definite trend of a greater lethality for the night group than the day group It also appeared that groups 4 and 9 had a lower mortality rate

A chi squared test was done to compare the lethality of the total day group with the total night group The $\chi^2_T = 11\ 14$ with one degree of freedom gave a significant differences of $0\ 001 > P$

A comparison between the day low mortality group 4 with group 3 just preceding it, gave $\chi^2_T = 1\ 78$, and with 1 degree of freedom was $0\ 25 > P > 0\ 10$

Then groups 3 and 5 were compared to group 4 This gave $\chi^2 = 3.05$ and with 1 degree of freedom was $0.10 > P > 0.05$ This calculation was done to determine if group 4 was significantly different from the other day groups

The same comparison was done for the night group, 9 compared to 10 χ^2_T equaled 3 50 and with 1 degree of freedom was $0.10 > P > 0.05$ However when groups 8 and 10 were compared to 9 $\chi^2_T = 7.63$ and with 1 degree of freedom the result was significant $0.10 > P > 0.005$

All the values of the day group were individually compared and the variations from one group to another proved that it could be random

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SUMMARY

Using 400 Swiss Webster male mice 14 weeks old an investigation was undertaken to determine their variation in sensitivity to radiation as a function of the time of day as measured by their death rate Twelve groups were exposed to 800 R with 280 kV roentgen rays HVL 2 0 mm Cu at two-hour intervals Using chi square tests the night group as a whole appeared more sensitive than the day group as a whole 0 001 P The variations within the day and night groups were not considered to be significant

ZUSAMMENFASSUNG

Es wurde an 400 vierzehn Wochen alten mannlichen Mausen untersucht inwieweit zu verschiedenen Tageszeiten eine Verschiedenheit der Strahlenempfindlichkeit besteht Dies wurde durch die Totlichkeitsrate ausgedruckt Zwolf Gruppen erhielten eine Strahlendosis von 800 R mit 280 kV HVL 2 0 Cu mit zweistundigen Intervall Unter Verwendung von chi square tests ergab sich dass die ganze Nachtgruppe strahlensensitiver als die Tagesgruppe war (0 001 P) Die Unterschiede innerhalb der Tages und Nachtgruppen waren nicht signifikant

RÉSUMÉ

L auteur a étudié sur 400 souris males Swiss Webster agées de 14 jours les variations de leur radiosensibilité en fonction du moment de la journée mesurée par leur taux de mortalité Douze groupes ont été exposés a 800 R de rayons roentgen de 280 kV et de C D A 2 mm Cu à des intervalles de deux heures Les tests chi² ont montré que l ensemble des groupes irradiés la nuit est plus radiosensible que l ensemble des groupes irradiés le jour avec une probabilité de 0 001 Les variations a l intérieur des groupes de jour et de nuit n ont pas été considérées comme significatives

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STRAUBE R L Examination of diurnal variation in lethality in irradiated rats Science 142 (1963) 1062

FROM THE DEPARTMENT OF RADIOBIOLOGY, CENTRE D'ETUDE DE L'ENERGIE NUCLEAIRE, MOL, BELGIUM

ROENTGEN IRRADIATION EFFECTS ON MOUSE PROTEINS

by

A. SASSEN, F. KENNES and J. R. MAISIN

JACOBSON et coll. (1951), LORENZ et coll. (1951) and many others have shown that bone marrow transplantation into lethally irradiated animals may prevent death. Whereas isogenic bone marrow gave about 100 % recovery in mice, transplantation of allogenic hematopoietic tissues prevented only acute radiation death during the initial 2 to 3 weeks and many animals died from a secondary disease during the subsequent months.

In view of the importance of the secondary disease and the uncertainties that still exist in this field, we have undertaken an extensive study on serum proteins of mice after roentgen irradiation and bone marrow transplantation. Some work has already been done in this field; only the effects of roentgen irradiation will be considered in this paper.

MATHÉ et coll. (1959) reported an increase in alpha$_2$ globulins and a concomitant decrease in albumin and gamma globulins after different doses of roentgen rays in mice. The gamma globulins levels and weight of spleen or lymph nodes were related by a correlation coefficient of + 0.74

Part of the results were presented at the 2nd Intern. Congress of Radiation Research, Harrogate 1962. Submitted for publication 15 January 1965.

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Table

Experiments performed

Roentgen doses in R	Number and strain of mice used			
	C	C57Bl	AK	CBA
500 (+)	—	23	—	—
600 (+)	30	33	—	—
650 (+)	—	10	—	—
700	10	6	—	—
750	30	68	10	—
800	9	10	21	—
850	—	—	37	—
900	72	10	15	—
1000	—	—	—	90

(+) Sublethal doses

The day before irradiation the mice were bled, analysis of the serum yielded values which were taken as normal and considered equal to 100 % Mice were whole body irradiated with a single dose of roentgen rays (from a G E Maxitron 300, 200 kV 20 mA HVL 1 mm Cu, target distance 50 cm dose rate 58 R/min) as indicated in the Table The mice were separated in groups of two to ten which were bled alternately either each day or all 2 to 3 days until death After sublethal doses the mice were followed in the same way during 1 to 2 months Each serum was analysed separately and the results expressed as percentages of the normal value Irradiated mice were placed individually in a cage and followed separately in some experiments As only *small differences between the different strains of healthy mice treated* similarly appeared after roentgen irradiation, all the data obtained were pooled Bacteriologic examination of heart blood was performed in some irradiated mice for the presence of pseudomonas or Proteus bacteria

Results

Control groups

Nonirradiated mice of the different strains were bled every day, the amount of blood taken being 50 to 70 mm³ Total proteins and electrophoretic analysis were performed on the sera After 4 to 6 bleedings of the same mouse, a decrease of 10 % in hematocrit value and of 10 to 15 % in total proteins was observed These values returned to a normal level even after further bleedings, no significant modifications in the EG patterns were observed

A similar fall of gamma globulins occurred one week after 300 R, but no changes in albumin, alpha or beta globulins were evident after this dose (ref 25) In F_1 hybrid mice irradiated with 950 R, total proteins and albumin decreased, whereas glycoproteins' (alpha globulins) and 'lipoproteins' (beta and gamma globulins) increased (ref 24) After the same dose of irradiation, C_3H mice displayed a considerable increase of an $alpha_2$ globulin, this protein seems to originate from cellular damage in the whole body without specific contributions from the liver or thymus (ref 4) GRABAR et coll (1963) published data on the modifications found by immunoelectrophoresis in the serum of roentgen irradiated mice, they found not only a decrease in prealbumin, $alpha_1$ and some beta and gamma globulins, but also new precipitation lines in the region of the $alpha_2$ globulins and a general increase of these fractions as well as of beta globulins The first alteration of serum proteins after irradiation was a rapid transformation of $beta_{1-C}$ to $beta_{1-A}$

Microelectrophoresis on agar gel (EG) and immunoelectrophoresis (IE) were used for the present study on serum protein modifications

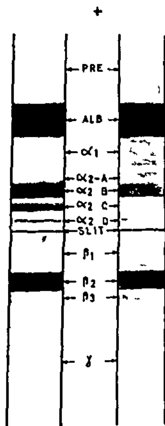


Fig 1 Agar gel microelectrophoresis patterns from normal (right) and irradiated (left) mouse serum

Contradictory and unreproducible results gradually occurred, these were traced to infections and in part suppressed by chlorination of the drinking water (ref 22) The observations were therefore extended over a period of more than two years in order to exclude as much as possible erroneous results from the true roentgen induced modifications

Methods Male mice of C57Bl/Rij, CBA/Rij AK and C_3 strains, 10 to 12 weeks old, were used throughout this work Electrophoretic technics were those previously described (ref 20) except for some minor modifications EG was performed at 14° C with a veronal buffer of pH 8 55 (unless otherwise stated), the fractions found by this method are indicated in Fig 1 Blood was obtained according to the technic of RILEY (1960) Total proteins and albumin were determined by UV absorption and partial elution (ref 20) or by the biuret methylorange method of KEYSER (1962)

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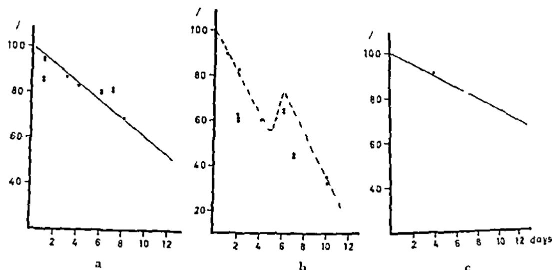


Fig 2 Modifications following lethal roentgen doses Each point is the mean of 2 to 10 mice (lines fitted visually) a) Total proteins b) Prealbumin general pattern (dashed line indicates the evolution in one experiment c) Albumin

Irradiated animals

Protein modifications depend upon the initial health of the mice, the changes of each fraction for infected and for non infected animals will therefore be presented separately The general pattern of roentgen induced modifications in healthy mice is depicted in Fig 1

1 *Total proteins* A progressive decrease until death was observed in lethally irradiated mice, at that time, the total protein levels had fallen to about 60 % of the normal value (Fig 2a) Infection seemed to be without influence on this modification A small decrease to 80 to 90 % occurred around the 8th to 12th day with return to a normal level after 5 to 6 weeks after sublethal irradiation

2 *Prealbumin* A decrease in the prealbumin level represents the general pattern after lethal roentgen doses (Fig 2b) A rapid fall to 50 to 60 % occurred in some animals shortly after irradiation, then an increase to 70 to 90 % during the 4th to 7th day, followed by a regular decrease until death, when concentrations of 20 to 30 % were observed This prealbumin decrease (with or without a peak around the 5th to 6th day) was evident in about 80 % of the experimental groups although in 20 % the fall in the prealbumin level did not occur The abnormal evolution seemed to be unrelated to the roentgen doses, strains of mice or apparent infections

Fig 3 Changes in α globulins after irradiation Agar gel microelectrophoresis performed at pH 8 45 (a) and at pH 8 55 (b)

After sublethal doses of irradiation, the prealbumin decreased to 50 to 60 % during the 10th to the 18th day Recovery then occurred, and a return to 100 % values was seen after 5 to 6 weeks

Infection produced the following changes C57Bl mice irradiated with 750 R and infected with *B pseudomonas* had a distinct increase in prealbumin which reached 140 % after 4 days in this experiment, the evolution of prealbumin was similar to that observed in the γ globulins In another group of the same strain irradiated with the same roentgen dose the prealbumin followed the normal pattern (decrease — small increase on the 5th day — decrease until death) whereas the γ globulins showed an irregular but clear increase heart blood cultures revealed *B proteus* In summary infected mice had increased values of prealbumin as reported by WILLIAMS & WEYMYSS (1961) in spite of radiation damage

A sharp decrease or sometimes a complete disappearance of the prealbumin was observed by IE only one week after lethal irradiation in 80 % of healthy mice (see Fig 6) On the other hand, the precipitation line was normal or slightly increased in the serum of infected animals

3 *Albumin* (Fig 2c) The albumin levels decreased to about 80 % in infected as well as in non infected mice after irradiation The values increased after

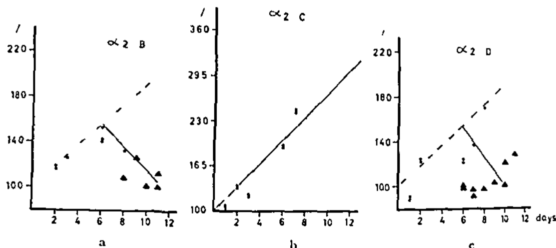


Fig 4 Modifications of the α_2 globulins after lethal irradiation a) Main changes (●) and accessory modifications (▲) of α_2—B globulins b) α_2—C globulins c) α —D globulins

two weeks and reached normal levels after 3 to 4 weeks after irradiation in sublethally irradiated mice

4 *Alpha$_1$ globulins* (Fig 3) LG generally revealed a decrease in this fraction during the first 10 days to about 50 to 60 % This level was reached at the time of death in lethally irradiated mice but after sublethal irradiation it returned to 100 % in about a month An initial slight increase or large variations were occasionally observed These abnormal results could be explained to some extent by the technical conditions of electrophoresis The pH of the buffer, originally at 8 45, was raised to 8 55 The α_1 globulins, composed of several fractions are better separated from albumin at a more basic pH When LG was performed at pH 8 45, a slight increase of α_1 globulins occurred after irradiation, on the other hand, a decrease was observed at pH 8 55 It may be assumed that the fast fractions, which are the most concentrated, decrease after irradiation, whereas the slow fractions increase If the separation of the α_1 globulins from the albumin zone is more complete (at a more basic pH), the decrease of the fast fractions will more than compensate the increase of the slow proteins

This hypothesis was confirmed by IL a decrease of $\alpha_{1-I\ II\ III}$ and an increase of α_{1-IV} were recorded Two precipitation lines were sometimes seen, more often in irradiated than in control mice the first was a fast moving component (α_{1-I})? and the second, a short line in the slow α_1 region These two proteins have not yet been identified

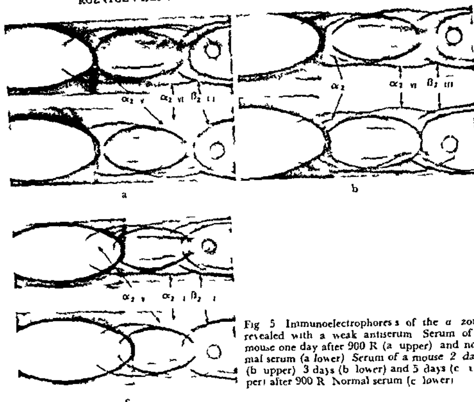


Fig 5 Immunoelectrophoresis of the α zone revealed with a weak antiserum Serum of a mouse one day after 900 R (a upper) and normal serum (a lower) Serum of a mouse 2 days (b upper) 3 days (b lower) and 5 days (c upper) after 900 R Normal serum (c lower)

5 *Alpha$_{2-A}$ and alpha$_{2-B}$ globulins* Lethal doses of irradiation produced a small increase of α_{2-A} during the first days and an irregular later decrease, corresponding modification was evident in the IE for the α_{2-I} line The data were too irregular to give conclusive results in sublethally irradiated mice

After high roentgen doses the α_{2-B} globulins increased markedly and reached levels of 150 % on day 6 (Fig 4a) in about 20 % of these mice a decrease occurred 2 or 3 days before death In sublethally irradiated mice levels increasing to 130 to 150 % during the first week were followed by a return to normal values after about one month

IE revealed normal appearances of the α_{2-II} globulin with occasionally an increase of the α_{2-III} or α_{2-IV} lines

6 *Alpha$_{2-C}$ globulins* As early as one day after lethal irradiation EG demonstrated an increase in this fraction (Fig 4b) after a week values up to 2 3 or even 4 times the normal level were observed After sublethal irradiation a return to the initial value occurred after 3 weeks



Fig 6 Immunoelectrophoresis from a normal mouse serum (upper) and from a mouse 10 days after 850 R (lower)

With respect to the IE analysis the difference in the appearances between a relatively weak and a strong antiserum must be distinguished In the former the α_{2-X} line grew to the anodic side as early as 12 hours after lethal irradiation, then moved aside the α_{2-II} line, increased more towards the anode, and crossed the α_{2-I} line so that its front end lay near the anodic part of the α_{2-I} (Fig 5) These modifications were less marked with a strong antibody against the α_2 region, the normal α_{2-X} line was increased in size and in intensity with an end near the α_{2-I}, in irradiated mice serum, only an increased concentration without a real change in mobility was evident (Fig 6)

Some specific reactions were tried in order to investigate this fraction The addition of a small amount of hemoglobin brought no changes (ref 7) When tested by the benzidin reaction, two lines, α_{2-X} and α_{2-XI}, disclosed peroxydase activity but ceruloplasmin was not revealed by staining with p phenylenediamin Autoradiography of IE performed after addition of ^{59}Fe hemoglobin (ref 19) to the serum showed 3 labelled lines, one α, the α_{2-X} line (considered actually as haptoglobin), and 2β lines (Fig 7) These lines are the β_{2-II} (possibly) and the β_{2-III}, one of them might be hemopexin but information about these lines is vague

7 *Alpha $_{2-D}$ globulins* This fraction increased to a smaller extent than the α_{2-C} and values of 140 % were obtained 6 days after lethal irradiation (Fig 4c) A return to the normal level occasionally occurred at the time of death and was evident after 3 weeks in sublethally irradiated mice A consistent IE finding was an increase of the α_{2-XI} line, since this fraction is a non hemin compound with oxidase activity it is probably ceruloplasmin, as suggested by HOCHWALD et coll (1961)

The α_{2-XII} line when visible (see Fig 6) was stronger in irradiated mice

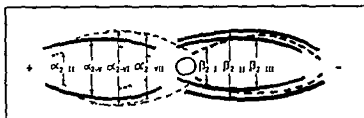


Fig 7 Radioautographic scheme of immunoelectrophoresis of a mouse serum incubated with Fe hemoglobin (continuous lines are radioactive dotted lines are not)

than in the controls but splitting, as described by GRABAR et coll (1963) was never observed

8 *Beta$_1$ and beta$_2$ globulins* Since the β_1 globulins are situated near the slit their levels are variable but seem to decrease slightly after irradiation No conclusive results were however obtained by EG or IE

Although the two β_2 fractions may generally be distinguished by EG, they will be considered as a whole Lethal irradiation produced a moderate increase which reached values of about 150 % in a week Sublethally irradiated mice were similarly, although somewhat later affected with a return to initial values between the 20th and the 30th day Infection seemed to be without influence on these modifications As GRABAR et coll (1963) pointed out IE analysis of this zone revealed an increase of some fractions and a decrease of others (Fig 6) Fraction β_{-III} increase the most a few days after irradiation its precipitation line went into the α_2 globulins this might have indicated a change in mobility although a cross reaction between β_{2-III} and the α_{2-V} line sometimes seemed to exist Increase of this fraction together with a variation of its mobility has been also described in the serum of mice suffering from plasma cell leukemia (ref 1)

The β_{2-I} (transferrin) was slightly increased

Two other fractions decreased after irradiation The β_{2-II} still visible 4 to 6 hours after a dose of 900 R, decreased after 8 hours and completely disappeared after 12 hours A similar change occurred in the β_{2-IV} ($\beta_{2\ \ XI}$) this protein was still present after 12 hours later it decreased and disappeared completely 24 to 36 hours after treatment

9 *Beta$_3$ globulins* A small decrease occurred generally at the 4th or 5th day followed either by a new increase or by a more marked decrease after a



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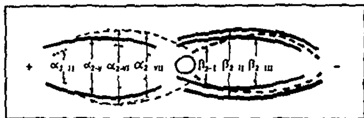


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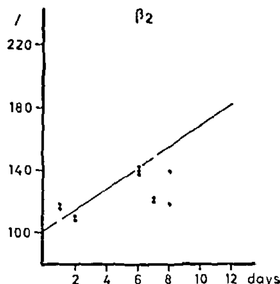


Fig 8 Changes in the β_2 globulins concentrations after irradiation

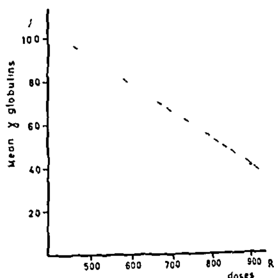


Fig 9 Regression line between roentgen doses and mean gamma globulins level in % of controls

transient increase during the first days These modifications were not related to the roentgen dosage, mice strains or infections

The cathodic end of the biphasic line of β_{3-1} was often increased (Fig 6) although an increase in the other part of the line was also encountered, these modifications were evident only one or two days after irradiation IE performed on the serum of infected mice always revealed a marked increase of the cathodic part of the β_{3-1} (ref 26)

10 *Gamma globulins* These proteins were considerably altered by irradiation (Figs 9 and 10) A decrease in the γ globulins in healthy mice could be detected as early as 24 hours after a large roentgen dose and was obvious after 2 days, levels of 10 to 15 % of the normal values were obtained at the time of death The γ globulins began to decrease on the 3rd day and reached levels of about 50 % after 1 or 2 weeks in sublethally irradiated mice an increase to normal values within a month then occurred

Mice with *B pseudomonas* septicemia had in spite of irradiation, a striking increase in these fractions, in *B proteus* infected animals, the early increase was followed by a fall, a decrease that never reached the level observed in healthy irradiated mice

The relation between the average decrease in γ globulins of healthy mice and roentgen doses between 500 R, the lowest dose of irradiation studied,

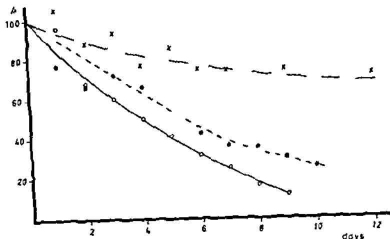


Fig 10 Relation between gamma globulins decrease and the time for different roentgen doses (○) 8 0 to 900 R (●) 750 to 800 R (×) 00 to 6 0 R

and 900 R seems to be linear (Fig 9) A correlation coefficient of — 0 78 (P < 0 01) was thus obtained

If the gamma globulin concentrations in mice irradiated with different roentgen doses are plotted against time curvilinear lines may be drawn through the experimental points The data are pooled in Fig 10 according to three ranges of roentgen doses Accepting that synthesis of γ globulins by lymphoid tissues is almost completely stopped after irradiation by 850 to 900 R the time needed for a decrease in γ globulins concentration from 100 % to 50 % *will be four days which is close to the half life of 4 6 days suggested* by Humphrey & Fahey (1961) for normal mouse γ globulins

A decrease of γ globulins with sometimes almost complete disappearance was also observed by IF in the serum of healthy lethally irradiated mice (Fig 6) The β_{3-II} and the β_{3-III} globulins appeared to decrease more slowly than the γ globulins but this point is very difficult to estimate without specific antisera against these fractions After sublethal roentgen doses the β_{3-III} globulin seemed to recover in the same way as the γ globulins whereas the β_{3-II} was restored more rapidly and became visible already at 15 days after 600 R

Immunoelectrophoresis in infected mice confirmed the data obtained by agar gel microelectrophoresis

11 *IE study with an antiserum against the serum from irradiated mice* Rabbits were injected with serum taken either from mice 4 days after a roentgen

dose of 900 R or from mice 3 days after a dose of 1 200 R, in order to find out whether special proteins appeared in the serum of lethally irradiated mice The antisera were individually tested and then pooled together without any concentration These antisera reacted with most of the serum proteins and especially with the α proteins but failed to develop prealbumin, β_{2-II} and β_{2-IV}

These antisera, when used against the sera of irradiated mice bled at different times after irradiation (6, 8, 10, 12, 14, 48 hours and 5, 6 days after 500, 700 or 900 R and 14 days after 600 R), never revealed a precipitation line not present in the normal sera

No special protein could thus be detected in the sera of irradiated mice

12 *Early effects of irradiation on mouse serum proteins* The following changes were generally observed by IE of the serum after whole body irradiation with a lethal roentgen dose a *gradual decrease of* β_{2-II} *and a small increase of* α_{2-V} from 6 to 8 hours, sometimes a slight decrease in the γ globulins and in the prealbumin from 10 to 12 hours, the β_{-IV} decreased, whereas the β_{2-III} and perhaps the β_{3-I} increased slightly, from 14 hours, after one day, an increased α_{2-V} and β_{2-III}, as well as the rather complete disappearance of β_{2-IV} and β_{2-II} and the decrease in γ globulins, were evident

The above appearances are obviously roughly drawn since each mouse will not be affected to the same extent and particularly will not respond at the same rate to radiation damage

The increase in β_{2-III} *and the decrease in* γ *globulins* were the latest modifications to disappear in sublethally irradiated mice

13 *Mobility changes* No obvious changes in the relative mobility of the serum proteins of irradiated mice, except for γ globulins were demonstrated by EG, but it has been shown previously (ref 20) that these modifications, because their mobility varies with concentration, are of little significance IE disclosed an increased mobility of α_{2-V} and β_{2-III} without any changes in the corresponding zones in the EG

Discussion

Two kinds of modifications (see Fig 1) appeared in the serum proteins of irradiated mice, some fractions increased whereas others decreased

The drop of γ globulins is probably related to extensive damage to the lymphoid organs The same mechanism could be valid for the decrease in β_{2-II} and β_{2-IV}

A similar change occurring in total proteins prealbumin, albumin, and in some α_1 globulins (all of which are synthesized supposedly by the liver), could be explained on the basis of two different hypotheses The first one would involve decreased synthesis due to cellular alterations or to the absence of some factors essential for protein synthesis the increase of other proteins like the α_2 globulins, which are also synthetized by the liver would then be difficult to explain, however On the other hand synthesis could proceed normally, but catabolism of some proteins could be increased either by activation of certain proteolytic enzymes or by intestinal loss Preliminary results on amino acid incorporation into proteins of irradiated or transplanted animals as well as the results of FRIEDBERG on serumalbumin metabolism (1960) and of SHABER & MILLER on fibrinogen (1963) are in favour of this explanation

A decrease in the prealbumin constitutes an unexpected roentgen effect PEETOM & KRAMER (1962) called it a sensitive indicator of protein balance, they found by IE equal modifications in the two prealbumin fractions (rho 1 and rho 2) It is not possible from the present results to establish whether these two fractions are equally affected by irradiation some tests with lipo protein stains suggest that lipoprealbumin (rho 2) decreases less after irradia tion than the trytophan rich prealbumin (rho 1)

None of the modifications observed is specific for radiation damage a general increase of α_2 globulins often appears in normal or tumour growth (ref 2) amyloidosis (ref 16) surgical trauma (ref 14), and infection (ref 2b) An increase in haptoglobin (ref 10) or in ceruloplasmin (ref 17) may also occur A change in β_{2-III} globulin identical with the present observation was described by CLAUSEN et coll (1959) in mice carrying plasma cell leukemia The γ globulins decrease is maybe the most specific change after irradiation

We did not succeed in identifying new precipitation lines in irradiated mouse serum as reported by GRABAR et coll (1963) There are also other small differences between the respective results These discrepancies could be explain ed by the differences in pH buffers in mouse strains, in roentgen doses and, especially in the immunserum

The patterns of protein alterations present in the serum of sublethally irradiated mice during the first 1 or 2 weeks was the same but less marked than the one observed after lethal roentgen doses The main difference between the two groups is the recovery that occurs after sublethal irradiations, with a return to the normal protein pattern

The early modifications evident in these two groups of mice are in disagree ment with the behaviour in rats in which different roentgen doses produced divergent modifications (ref 21)

One thing must be stressed Notwithstanding the maximum control of the

known factors involved in these experiments (inbreeding of mice, roentgen doses, electrophoretic techniques), the results obtained from one experiment to another were not completely reproducible Two factors seem responsible for this variation The first is related to the mice their health, including nutritional conditions and, especially, latent infections would have been completely controlled This could be achieved only with germ free or, at least, with pathogen free animals The second factor concerned the poor reproducible determination of certain protein fractions such as prealbumin, a_{2-m}, β_1 and β_2 globulins by agar electrophoresis Immunologic precipitation methods with specific antisera would be very useful for these proteins

Acknowledgements

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SUMMARY

Serum protein changes in whole body irradiated mice are described A correlation was found between the decrease in the γ globulins concentrations and the roentgen dose Some change in the immunoelectrophoretic pattern was evident as early as at 6 to 8 hours Certain abnormal alterations in the protein pattern of irradiated mice appear to be related to infection

ZUSAMMENFASSUNG

Die Änderungen des Serumproteingehaltes nach Totalbestrahlung von Mausen werden beschrieben Eine Beziehung zwischen der Abnahme der γ Globulinwerte und der Rontgen dose konnte festgestellt werden Schon bei 6 bis 8 Stunden nach der Bestrahlung wurden Veranderungen des immuno elektrophoretischen Verhaltens gefunden Bestimmte abnormale Proteinwerte von totalbestrahlten Mausen sind durch Infektion bedingt

RÉSUMÉ

Description des modifications des protéines du sérum chez des souris après irradiation du corps entier On a trouvé une corrélation entre la baisse de la concentration des γ globulines et la dose d irradiation roentgen Le diagramme d immuno électrophorèse est un peu modifié dès la 6ᵉ ou 8ᵉ heure Certaines altérations anormales du protéinogramme de souris irradiées semblent être dues à une infection

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RETENTION OF STRONTIUM 85 IN RATS

II Effect of various barium sulphate preparations as influenced by soluble sulphates, carrier strontium and by the physiologic state of animals

by

VLADIMIR VOLF and ZDENEK ROTH

Considerable decrease in the retention of ^{85}Sr given orally can be achieved if the administration is shortly followed by a mixture of barium and sodium or magnesium sulphates (VOLF & ROTH 1965) Conditions during precipitation are especially important in the preparation of the barium sulphate the resultant particles may be of different size and shape and the physico chemical properties may also differ (LIFSER & FABRIKANOS 1959 SUITO & TAKIYAMA 1954) The authors have therefore determined the ability of various barium sulphate preparations alone or in the presence of soluble sulphates to bind radiostrontium in vitro and in vivo

The effect of the isotopic carrier and of certain physiologic factors (presence of food in the gastrointestinal tract maturity of animals) has also been studied

Methods

Barium sulphate Barium sulphate (preparation I) precipitated from boiling 0 5 M solutions of barium hydroxide and sulphuric acid was used as in the

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Table 1 *(cont.)*

				Anions (mg/kg)				
Ca	Mg	Fe	Al	HCO	Cl	SO	NO_3	H SiO
371	5483	—	12	1090	3.9	23828	2642	—
382	2870	0.3	—	*117*	*304*	*23060*	—	21

The isotopic carrier was added either to the radiostrontium or the sulphates. *To the sodium sulphate 10 μM of Sr^{2+} ions* in the form of strontium chloride were added. No visible precipitation of strontium sulphate appeared in vitro. *Ten and 100 μM Sr^{2+} ions were added to the barium sulphate.*

The effect of sulphates in fasting and feeding rats (weighing 170 to 200 g) *was investigated in two experiments.* In the first experiment half the number of animals were deprived of food 20 hours before and the others were normally fed. In the second *experiment food was withdrawn from all the animals.* Half the number of rats were fed one hour before the start of the experiment *on a weighed quantity of standard diet which was withdrawn half an hour* later.

The effect of sulphates in rats of various ages (which has been estimated according to their bodyweight — Table 6) was studied in three experiments. *Doses and volumes have been adjusted according to the difference in body* weight so that young and adult animals each received the same quantity of ^{85}Sr and sulphates per kg bodyweight. In the first experiment 3.8 mM of barium sulphate (preparation II), in the second and third 8.9 mM and 7.6 *mM of barium sulphate* (preparation *III*) respectively, with equimolar doses of sodium sulphate were administered per kg bodyweight.

Two Czechoslovak natural mineral waters (see *Table I*) containing a considerable amount of sodium and magnesium sulphates alone and in com*bination with barium sulphate* (1.6 mM per dose) were also tested. One dose (3 ml) of mineral water contained about 0.7 mM of sodium and magnesium sulphates.

Results

Various barium sulphates. Examination with an electron microscope (Figs 1 and 2) *proved that the particles of* preparation *II* are considerably larger than those of preparation I, so that it can be assumed that the inner surfaces

Table 1

The chemical contents of Czechoslovak bitter mineral waters

Mineral water	Evaporation residue (mg/l)	CO_2 (mg/l)	Cations (mg/kg)		
			Na	K	Sr
Zaječická horká (Middle Bohemian Springs)	36027	—	2159	81	3
Šaratica (Moravian Silesian Springs)	36220	103	7040	49	—

previous experiments (VOLF & ROTH 1965) The possibly disturbing influence of further ions during precipitation was thus avoided, sulphuric acid was added in excess and the precipitate was repeatedly washed and tested for free barium and sodium ions

Barium sulphate (preparation II) was prepared in the same way, only barium chloride was used instead of barium hydroxide and the precipitate was very thoroughly boiled The contrast medium Skiabaryum (Slovakofarma, CSSR), as well as the barium sulphate used in its preparation, were tested, this preparation III complies with the regulations of the Czechoslovak pharmacopoeia on chemical purity

In vitro experiments The sorptive capacity of the above barium sulphate preparations was tested, carrier free ^{85}Sr chloride solution being added to 100 ml of 0 4 % water suspension of the sorbent The water suspension of sulphate with added ^{85}Sr was shaken at half hourly intervals three times and then left standing at room temperature Twenty hours after adding ^{85}Sr, two 1 ml aliquots of supernatant were collected and assayed by a well type scintillation counter The decrease of the activity in the solution with the sorbent present was compared with the radiostrontium standard and expressed as a percentage of the added activity The sorption was followed up on barium sulphate alone, as well as after that the equimolar quantity of sodium sulphate had been added

Animal experiments Details of the procedure have been reported previously (VOLF & ROTH 1965) Two hundred male Wister albino rats received orally 1 to 2 μCi of ^{85}SrCl in 0 1 ml of liquid, and 10 min later 0 8 mM of each sulphate in 2 ml distilled water Whole body counting was made 15 min after the administration of ^{85}Sr and repeated 24 and 48 hours later, when the animals were sacrificed The ^{85}Sr in the dissected femurs was determined The results were expressed as percentages of the ^{85}Sr dose administered

Table 1 *(cont.)*

				Anions (mg/kg)				
Ca	Mg	Fe	Al	HCO	Cl	SO_4	NO_3	H SiO
371	5483	—	12	1090	359	23828	2642	—
382	2870	0.3	—	117	304	23060	—	25

The *isotopic carrier was added* either to the *radiostrontium* or the sulphates. To the sodium sulphate 10 μM of Sr^{2+} ions in the form of strontium chloride were added. No visible precipitation of strontium sulphate appeared in vitro. Ten and 100 μM Sr^{2+} ions were added to the barium sulphate.

The effect of sulphates in fasting and feeding rats (weighing 170 to 200 g) was *investigated in two experiments*. In the first experiment half the number of animals were deprived of food 20 hours before and the others were normally fed. In the second experiment food was withdrawn from all the animals. Half the number of rats were fed one hour before the start of the experiment, on a weighed quantity of standard diet which was withdrawn half an hour later.

The effect of sulphates in rats of various ages (which has been estimated according to their bodyweight — Table 6) was *studied in three experiments*. Doses and *volumes have been adjusted* according to the difference in body weight so that young and adult animals each received the *same quantity of* ^{85}Sr and sulphates *per kg bodyweight*. In the first experiment 3.8 mM of *barium sulphate* (preparation II) in the second and third 8.9 mM and 7.6 mM of barium sulphate (preparation III) *respectively, with* equimolar doses of sodium sulphate *were administered* per kg bodyweight.

Two Czechoslovak natural mineral waters (see Table 1) containing a considerable amount of sodium and *magnesium sulphates* alone and in combination with *barium sulphate* (1.6 mM per dose) were also tested. One *dose* (3 ml) of mineral water contained about 0.7 mM *of sodium* and magnesium sulphates.

Results

Various barium sulphates. Examination with an electron microscope (Figs 1 and 2) proved that the particles of preparation II are *considerably* larger than those of preparation I, so that *it can be assumed that the* inner surfaces

Table 1

The chemical contents of Czechoslovak bitter mineral waters

Mineral water	Evaporation residue (mg/l)	CO_2 (mg/l)	Cations (mg/kg)		
			Na	K	Sr
Zaječická hořká (Middle Bohemian Springs)	36027	—	2159	81	3
Šaratica (Moravian Silesian Springs)	36220	103	7040	49	—

previous experiments (VOLF & ROTH 1965). The possibly disturbing influence of further ions during precipitation was thus avoided, sulphuric acid was added in excess and the precipitate was repeatedly washed and tested for free barium and sodium ions.

Barium sulphate (preparation II) was prepared in the same way, only barium chloride was used instead of barium hydroxide and the precipitate was very thoroughly boiled. The contrast medium Skiabaryum (Slovakofarma, CSSR), as well as the barium sulphate used in its preparation, were tested; this preparation III complies with the regulations of the Czechoslovak pharmacopoeia on chemical purity.

In vitro experiments. The sorptive capacity of the above barium sulphate preparations was tested, carrier free ^{85}Sr chloride solution being added to 100 ml of 0.4 % water suspension of the sorbent. The water suspension of sulphate with added ^{85}Sr was shaken at half hourly intervals three times and then left standing at room temperature. Twenty hours after adding ^{85}Sr, two 1 ml aliquots of supernatant were collected and assayed by a well type scintillation counter. The decrease of the activity in the solution with the sorbent present was compared with the radiostrontium standard and expressed as a percentage of the added activity. The sorption was followed up on barium sulphate alone, as well as after that the equimolar quantity of sodium sulphate had been added.

Animal experiments. Details of the procedure have been reported previously (VOLF & ROTH 1965). Two hundred male Wister albino rats received orally 1 to 2 μCi of ^{85}SrCl in 0.1 ml of liquid, and 10 min later 0.8 mM of each sulphate in 2 ml distilled water. Whole body counting was made 15 min after the administration of ^{85}Sr and repeated 24 and 48 hours later, when the animals were sacrificed. The ^{85}Sr in the dissected femurs was determined. The results were expressed as percentages of the ^{85}Sr dose administered.

Table 1 *(cont.)*

				Anions (mg/kg)				
Ca	Mg	Fe	Al	HCO	Cl	SO	NO	H_2SiO_3
371	5483	—	12	1090	359	23828	?642	—
382	2820	0 3	—	117	304	23060	—	21

The isotopic carrier was added either to the radiostrontium or the sulphates To the sodium sulphate 10 μM of Sr^{2+} ions in the form of strontium chloride were added No visible precipitation of strontium sulphate appeared in vitro Ten and 100 μM Sr^{2+} ions were added to the barium sulphate

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The effect of sulphates in rats of various ages (which has been estimated according to their bodyweight — Table 6) was studied in three experiments Doses and volumes have been adjusted according to the difference in body weight so that young and adult animals each received the same quantity of ^{85}Sr and sulphates per kg bodyweight In the first experiment 3 8 mM of barium sulphate (preparation II), in the second and third 8 9 mM and 7 6 mM of barium sulphate (preparation III) respectively with equimolar doses of sodium sulphate were administered per kg bodyweight

Two Czechoslovak natural mineral waters (see Table 1) containing a considerable amount of sodium and magnesium sulphates alone and in combination with barium sulphate (1 6 mM per dose) were also tested One dose (3 ml) of mineral water contained about 0 7 mM of sodium and magnesium sulphates

Results

Various barium sulphates Examination with an electron microscope (Figs 1 and 2) proved that the particles of preparation II are considerably larger than those of preparation I, so that it can be assumed that the inner surfaces

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Animal experiments. Details of the procedure have been reported previously (VOLF & ROTH 1965). Two hundred male Wister albino rats received orally 1 to 2 μCi of $^{85}SrCl_2$ in 0.1 ml of liquid, and 10 min later 0.8 mM of each sulphate in 2 ml distilled water. Whole body counting was made 15 min after the administration of ^{85}Sr and repeated 24 and 48 hours later, when the animals were sacrificed. The ^{85}Sr in the dissected femurs was determined. The results were expressed as percentages of the ^{85}Sr dose administered.

Table 1 *(cont)*

				Anions (mg/kg)				
Ca	Mg	Fe	Al	HCO	Cl	SO	NO$_3$	H$_2$SiO
371	5483	—	1?	1090	359	23828	2642	—
382	2820	0 3	—	117	304	23060	—	21

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Two Czechoslovak natural mineral waters (see Table 1) containing a considerable amount of sodium and magnesium sulphates alone and in combination with barium sulphate (1 6 mM per dose) were also tested One dose (3 ml) of mineral water contained about 0 7 mM of sodium and magnesium sulphates

Results

Various barium sulphates Examination with an electron microscope (Figs 1 and 2) proved that the particles of preparation II are considerably larger than those of preparation I so that it can be assumed that the inner surfaces



Fig 1 Barium sulphate (preparation I) in water suspension

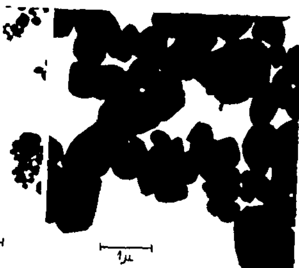


Fig 2 Barium sulphate (preparation II) in water suspension

of both samples also differ Figs 3 and 4 show preparation III and Skiabaryum, conglomerates of particles of the latter are larger than in preparation III in addition, hazy spots, probably particles of higher solubility, are evident in Fig 4

It is seen from Table 2 that the sorptive capacity of various barium sulphate preparations in vitro differed, but in the presence of an excess of the sulphate ions it always increased considerably

The results given in Table 3 indicate that after the administration of preparation I to rats, the average retention of ^{85}Sr in the whole body, as well as the content of ^{85}Sr in the skeleton, after 24 and 48 hours were markedly lower (by about 60 %) than after the administration of preparation II

Different barium sulphate preparations are compared in Table 4, on the basis of the calculated ratios of their effect in vitro as well as in vivo In estimating the effectiveness in vivo, the degree of decrease in the skeletal ^{85}Sr retention in rats after the oral administration of 0 8 mM barium sulphate, or its combination with 0 8 mM sodium sulphate, 10 min after contamination with ^{85}Sr (experiments reported above and in our previous communication), was taken into account The less effective means are shown in the upper half of the table, and it is evident that marked difference in the effect in vitro is necessary in order for them to appear in vivo as well The more effective means in the lower part of the table prove that the more they differ from each other in vitro the more obvious their difference in vivo The difference in the effect of the same preparation is usually more marked in vivo than in vitro

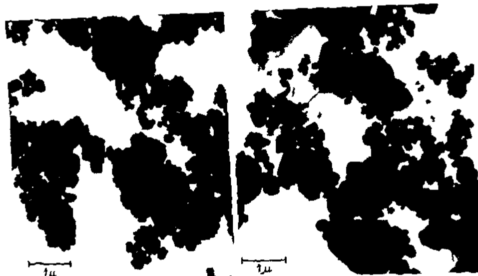


Fig 3 Barium sulphate (preparation III) in water suspension Fig 4 Skiabaryum in water suspension

Sulphates and carrier It may be seen from Table 5 that after the administration of ^{85}Sr and 10 μM carrier strontium as well as of sulphate without carrier strontium the variance of the average values of ^{85}Sr retention in the whole body as well as in the bones, increased The average effectiveness of barium sulphate after the administration of ^{85}Sr with 100 μM carrier strontium decreased in comparison with the group in which no carrier strontium was added This decrease is close to the significant value (for $p < 0.05$) There were otherwise no substantial changes in the average effect of sulphates after adding carrier strontium

The addition of isotopic carrier strontium to ^{85}Sr or to sodium or barium sulphates thus tended to decrease the average effect of barium sulphate only when ^{85}Sr with 100 μM carrier (largest carrier dose examined) was administered

Sulphates in fasting and fed rats Results of the two experiments are collected in Table 6 Substantially less ^{85}Sr was absorbed from the intestine of feeding than fasting animals Barium sulphate alone decreased the retention of ^{85}Sr only in the fasting rats on the others it had no effect The combination of barium and sodium sulphates decreased the average retention of ^{85}Sr after 18 hours to the same level in both groups Taking into consideration that the feeding control animals retained significantly less ^{85}Sr than the fasting animals



Fig 1 Barium sulphate (preparation I) in water suspension

Fig 2 Barium sulphate (preparation II) in water suspension

of both samples also differ Figs 3 and 4 show preparation III and Skiabaryum, conglomerates of particles of the latter are larger than in preparation III, in addition, hazy spots, probably particles of higher solubility, are evident in Fig 4

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Table 4

Effect of various barium sulphate preparations in vitro and in vivo

Substances tested	In vitro		In vivo	
	Percentage of Sr adsorbed	Ratio of effect	Percentage of Sr in the skeleton	Ratio of effect
BaSO I	62 2		7 4	
Skiabaryum	53 1	1 2	11 0	1 5 n.s
Sk abaryum	53 1		7 4	
BaSO III	40 4	1 3	8 5	1 1 n.s.
BaSO I	62 2		9 9	
BaSO II	21 8	2 9	23 7	2 4
BaSO I + Na SO_4	95 5		3 1	
Skiabaryum + Na SO	79 8	1 2	4 8	1 6
BaSO I + Na SO	95 5		4 9	
BaSO I	62 2	1 5	10 6	2 2
BaSO III + Na SO	86 6		2 2	
BaSO III	40 4	2 1	8 5	3 9

Rel tion of the percentage of Sr adsorbed on the more effective means to the percentage of Sr adsorbed on the less effect ve means

48 hours after Sr admini trat on — both compared values always result from the same experiment

R lation of the percentage of Sr reta ned after admin stration of the more effective means to the pe centage of Sr retained after administration of the less effective means

The d ff ence n effect is not statistically s gn ficant

An analogic but statistically not important difference was observed after the administration of 8 8 mM barium (preparation III) and sodium sulphates per kg bodyweight to rats 10 and 16 weeks old When 7 6 mM of barium (preparation III) and sodium sulphates per kg bodyweight were given young growing rats of 7 weeks retained 55 % more ^{85}Sr in their bones than adult animals of 20 weeks An analogic difference was apparent in control rats of various ages as far as the retention of ^{85}Sr was concerned

Mineral waters The whole body retention of ^{85}Sr decreased after the administration of bitter mineral waters by 40 % to 50 % and the skeletal content by 50 % to 60 % in comparison with the controls The average effect of both mineral waters was practically the same (Table 8) The retention of ^{85}Sr decreased further (*significantly*) when barium sulphate suspended in bitter mineral waters was administered (by 80 % to 85 % and by 80 % to 90 % in

Table 2

Adsorption of ^{85}Sr on Skiabaryum and various barium sulphate preparations in vitro (solution incubated 20 hours at room temperature with 0.4 % sulphate)

Preparation	Percentage of adsorbed ^{85}Sr	
	Barium sulphate	Barium and Sodium sulphate
Skiabaryum	53.1	79.8
Barium sulphates		
Preparation I	62.2	95.5
Preparation II	21.8	86.3
Preparation III	40.4	86.6

Table 3

Relative effectiveness of two barium sulphate preparations administered orally in doses of 0.8 mM 10 min after oral contamination with ^{85}Sr

Barium sulphate	Percentage of ^{85}Sr administered[1]	
	Whole body	Skeleton[2]
Preparation I	11.7 ± 3.8	9.9 ± 3.6
Preparation II	29.5 ± 5.7	23.7 ± 4.1

[1] Arithmetic mean ± standard error of the mean multiplied by t value for 95 % confidence level. Eight animals per group. 48 hrs after administration of ^{85}Sr

[2] Content of ^{85}Sr in 1 femur × 20

(by 70 %), there was of course a relatively more marked decrease after the administration of sulphates to the fasting animals (by 80 % and 90 % in the whole body and the skeleton, respectively) than to the others (by 40 % and 50 %, respectively).

Sulphates in young and adult rats. Results of three experiments are summarized in Table 7. The age difference between the groups compared was relatively small, i.e. from 6 to 13 weeks. Although the average retention of ^{85}Sr was repeatedly higher in the younger than in the older rats, the differences observed in the control rats of various ages were significant only in one of the experiments described.

After the administration of barium sulphate (preparation II) in doses of 3.8 mM per kg bodyweight, young animals of 7 weeks of age retained 50 % more ^{85}Sr in their bones than the adult rats of 20 weeks.

Table 6

Effe t of barium sulphate (preparation I) administered orally in doses of 0 8 mM 10 min after oral contamination with Sr to fasting and feeding rats

Substances tested	Number of animals	Percentage of ⁸Sr administered					
		Whole body				Skeleton[1]	
		After 24 hours		After 48 hours		After 48 hours	
		$\bar{x} \pm ts$ [2]	Percent age of control	$\bar{x} \pm ts$	Percent age of control	$\bar{x} \pm ts$	Percent age of control
Controls fasted	4	38 0 ± 32 9	100	27 8 ± 22 0	100	22 2 ± 17 9	100
Controls fed	4	19 0 ± 3 3	n s	14 9 ± 2 7	n s	9 7 ± 1 5	n s
BaSO fasted	4	17 4 ± 8 4	n s	8 6 ± 7 6	n.s	7 4 ± 6 7	n s
BaSO fed	6	20 8 ± 15 4	n s	11 5 ± 4 5	n s.	8 8 ± 3 5	n s
Controls fasted	6	45 5 ± 17 6	100	21 9 ± 10 8	100	16 9 ± 10 9	100
Controls fed	6	28 6 ± 5 1	n s	6 8 ± 2 9	31	4 6 ± 2 1	27
BaSO Na SO fasted	6	37 0 ± 14 1	n s	4 2 ± 2 2	19	1 7 ± 0 9	10
B SO Na SO fed	6	29 8 ± 19 0	n s	4 5 ± 1 4	20	2 2 ± 0 7	13

Content of Sr in 1 femur × 20
Ar thmetic me n ± standard e ror of the mean multipl ed by t value for 95 confidence level
Difference not tat stically s gnificant

is also a certain difference between preparation III and Skiabaryum the latter containing additional substances The microscopic appearances are in accord with the results of the experiments in vitro as well as in vivo where the effec tiveness increases in a reversed sequence in relation to the size of particles i e preparation II < preparation III < preparation I A somewhat higher percentage of ⁸⁵Sr is absorbed by Skiabaryum in vitro in comparison with preparation III This can be explained by the presence of bentonite with a high exchange capacity for radiostrontium in a neutral medium (KNAJFL 1963)

The sorptive capacity of all barium sulphate preparations was considerably improved by adding free sulphate ions This increase was more marked with the less effective means so that differences between various preparations dis appeared Their effectiveness in vivo in the presence of sodium sulphate also

Table 5

Influence of carrier strontium on effectiveness of sodium and barium (preparation I) sulphates administered orally in doses of 0.8 mM 10 min after oral contamination with ^{85}Sr

Isotopic carrier (μM Sr^{2+})		Number of animals	Percentage of ^{85}Sr administered[1]		
			Whole body		Skeleton[2]
^{88}Sr	sulphate		After 24 hours	After 48 hours	After 48 hours
	Sodium				
0	0	6	31.3 ± 8.3	18.6 ± 4.0	13.3 ± 3.7
0	10	6	39.5 ± 14.3	20.6 ± 6.3	14.1 ± 3.8
10	0	6	49.1 ± 23.5	24.2 ± 21.8	15.7 ± 11.5
	Barium				
0	0	6	43.8 ± 28.6	17.7 ± 7.3	12.5 ± 5.5
0	10	5	34.7 ± 10.7	23.3 ± 4.5	17.4 ± 4.4
0	100	5	37.6 ± 10.6	26.6 ± 5.6	17.0 ± 2.4
10	0	5	42.2 ± 13.1	24.5 ± 13.6	18.6 ± 9.1
100	0	5	44.5 ± 33.6	26.8 ± 9.3	19.0 ± 5.1

[1] Arithmetic mean ± standard error of the mean multiplied by t value for 95% confidence level

[2] Content of ^{85}Sr in 1 femur × 20

the whole body and in the skeleton, respectively, in comparison with controls). The average effect of barium sulphate suspended in Zaječická horká (Middle Bohemian Springs) was significantly better (by 50%) than in Saratica' (Moravian Silesian Springs) (For chemical composition of these mineral waters, see Table 1.)

Discussion

Barium sulphate preparations bind radiostrontium in vitro to a varying degree and this is reflected in various degrees of decontamination effectiveness in vivo. Many factors during the precipitation of barium sulphate are important, these include the concentration of Ba^{2+} ions in solution, the ratio of Ba ions to SO_4^{-}, the solvent, the age of the solutions used, the presence of foreign ions and other impurities and the method of precipitation, temperature, and other conditions (LIESER & FABRIKANOS 1959). Barium sulphate precipitates of various forms were obtained in this way by the effect of the concentration of the barium hydroxide and sulphuric acid used for precipitation (SUITO & TAKIYAMA 1954).

The electron microscope photographs of the present investigation are very similar to those of the Japanese authors. The barium sulphate particles are seen to grow, i.e. preparation I < preparation III < preparation II. There

Table 6

Effect of barium sulphate (preparation I) administered orally in doses of 0 8 mM 10 min after oral contamination with Sr to fasting and feeding rats

Substances tested	Number of animals	Percentage of Sr administered — Whole body — After 24 hours — $\bar{x} \pm ts$	Percentage of control	After 48 hours — $\bar{x} \pm ts$	Percentage of control	Skeleton — After 48 hours — $\bar{x} \pm ts$	Percentage of control
Controls							
fasted	4	38 0 ± 32 9	100	27 8 ± 22 0	100	22 2 ± 17 9	100
Controls fed	4	19 0 ± 3 3	n s*	14 9 ± 2 7	n s	9 7 ± 1 5	n s
BaSO							
fasted	4	17 4 ± 8 4	n s	8 6 ± 7 6	n s	7 4 ± 6 7	n s
$BaSO_4$ fed	6	20 8 ± 15 4	n s	11 5 ± 4 5	n s	8 8 ± 3 5	n s
Controls							
fasted	6	45 5 ± 17 6	100	21 9 ± 10 8	100	16 9 ± 10 9	100
Controls fed	6	28 6 ± 5 1	n s	6 8 ± 2 9	31	4 6 ± 2 1	27
BaSO Na SO							
fasted	6	37 0 ± 14 1	n s	4 2 ± 2 2	19	1 7 ± 0 9	10
BaSO Na SO							
fed	6	29 8 ± 19 0	n s	4 5 ± 1 4	20	2 2 ± 0 7	13

Content of Sr in 1 femur × 20

Arithmetic mean ± standard error of the mean multiplied by t value for 95 confidence level

Difference not statistically significant

is also a certain difference between preparation III and Skiabaryum the latter containing additional substances The microscopic appearances are in accord with the results of the experiments in vitro as well as in vivo where the effectiveness increases in a reversed sequence in relation to the size of particles i e preparation II < preparation III < preparation I A somewhat higher percentage of ⁸⁵Sr is absorbed by Skiabaryum in vitro in comparison with preparation III This can be explained by the presence of bentonite with a high exchange capacity for radiostrontium in a neutral medium (KNAJFL 1963)

The sorptive capacity of all barium sulphate preparations was considerably improved by adding free sulphate ions This increase was more marked with the less effective means so that differences between various preparations disappeared Their effectiveness in vivo in the presence of sodium sulphate also

Table 7

Effect of barium sulphate administered orally, alone or in combination with sodium sulphate 10 min after oral contamination with [85]Sr, followed in rats of various ages

Age group (body weight)	Substances tested (mM/kg b wt)	Number of animals	Percentage of [85]Sr administered					
			Whole body				Skeleton[1]	
			After 24 hours		After 48 hours		After 48 hours	
			$\bar{x} \pm ts_x$[2]	Percentage of control	$\bar{x} \pm ts_x$	Percentage of control	$\bar{x} \pm ts$	Percentage of control
7 weeks (70 g)	Controls	6	46 3 ± 20 4	100	38 4 ± 17 1	100	35 4 ± 18 7	100
	$BaSO_4$II (3 8)	6	36 2 ± 9 2	n s[3]	29 8 ± 2 7	n s	28 9 ± 8 0	n s
20 weeks (210—225 g)	Controls	6	50 2 ± 15 4	n s	34 2 ± 18 8	n s	26 4 ± 15 7	n s
	$BaSO_4$II (3 8)	6	31 7 ± 17 0	n s	20 4 ± 9 6	n s	14 5 ± 8 4	n s
10 weeks (100 g)	Controls	6	47 3 ± 0 6	100	36 8 ± 6 2	100	29 1 ± 5 4	100
	$BaSO_4$III + Na_2SO_4 (8 9)	6	29 2 ± 1 1	62	13 3 ± 5 7	36	10 1 ± 4 8	35
16 weeks (180—185 g)	Controls	6	41 0 ± 1 6	100	31 3 ± 12 4	100	26 6 ± 9 4	100
	$BaSO_4$III + Na_2SO_4 (8 9)	6	20 8 ± 1 0	51	9 5 ± 5 2	30	6 3 ± 3 5	24
7 weeks (70—80 g)	Controls	6	68 7 ± 9 9	100	52 4 ± 7 6	100	47 6 ± 5 6	100
	$BaSO_4$III + Na_2SO_4 (7 6)	6	18 8 ± 5 1	27	11 0 ± 2 2	21	10 5 ± 3 0	22
20 weeks (210—220 g)	Controls	6	45 0 ± 17 0	100	30 0 ± 9 6	100	26 1 ± 8 9	100
	$BaSO_4$III + Na_2SO_4 (7 6)	6	33 5 ± 9 6	74	7 1 ± 2 9	24	5 1 ± 2 3	20

[1] Content of [85]Sr in 1 femur × 20

[2] Arithmetic mean ± standard error of the mean multiplied by t value for 95 % confidence level

[3] Difference not statistically significant

differed only slightly Skiabaryum with sodium sulphate was the least effective of all the combinations tested in vitro and in vivo We assume a disturbing influence of other ingredients in Skiabaryum to be the cause but this could not be confirmed in the experiments

Many authors pay attention to the influence of a stable isotopic carrier

Table 8

Effect of saline bitter mineral waters and their combinations with barium sulphate (preparation III) administered orally 10 min after oral contamination with Sr

Substances tested	Number of animals	Percentage of Sr administered					
		Whole body				Skeleton	
		After 24 hours		After 48 hours		After 48 hours	
		$\bar{x} \pm ts$ *	Percentage of control	$\bar{x} \pm ts$	Percentage of control	$\bar{x} \pm ts$	Percentage of control
Controls	6	51 0 ± 10 4	100	43 9 ± 9 0	100	38 1 ± 8 0	100
Saratica	5	27 5 ± 11 7	54	21 5 ± 7 5	49	18 7 ± 6 9	49
Zaječická	5	23 7 ± 3 6	46	17 9 ± 3 6	41	14 1 ± 2 9	37
$BaSO_4$ + Saratica	5	14 0 ± 9 4	27	8 8 ± 4 9	20	7 9 ± 2 9	21
$BaSO_4$ + Zaječická	5	17 5 ± 11 2	34	6 6 ± 2 6	15	4 0 ± 1 4	11

Content of Sr in 1 femur × 20

Arithmetic mean ± standard error of the mean multiplied by t value for 95 confidence level

on the metabolism of radiostrontium This paper deals only with a carrier administered orally

COPP & GREENBERG (1944) observed that a large dose of carrier strontium (50 mg) had little effect on the intestinal absorption of ⁸⁹Sr in rats Whether on stock diet or on a diet low in calcium the animals retained less radio strontium only when administered simultaneously with carrier GROSS *et coll* (1954) administered to rats by stomach tube up to a hundred times the normal daily intake of stable strontium mixed with ⁹⁰Sr and ⁹⁰Y daily for seven consecutive days The amount of stable strontium used did not alter the uptake of ⁹⁰Sr JONES (1955) who administered radiostrontium orally in addition to varying amounts of carrier (1—500 µg) per gram bodyweight to fasting rats observed that the urinary radiostrontium increased threefold after the highest dose however the skeletal retention did not change in comparison with the controls RUBANOVSKAIA & USHAKOVA (1957) concluded that after the administration of ⁸⁹Sr by stomach tube followed immediately by treatment with strontium lactate (50 mg per rat per day) for twelve days the elimination of ⁸⁹Sr from the bone as well as from the whole organism was not substantially enhanced According to KHOMUTOVSKII (1959) a previous four day oral administration of strontium nitrate (100 mg per diem) does not increase the elimination of ⁹Sr in rats

Table 7

Effect of barium sulphate administered orally, alone or in combination with sodium sulphate 10 min after oral contamination with ⁸⁵Sr followed in rats of various ages

Age group (body weight)	Substances tested (mM/kg b wt)	Number of animals	Percentage of ⁸⁵Sr administered					
			Whole body				Skeleton[1]	
			After 24 hours		After 48 hours		After 48 hours	
			$\bar{x} \pm ts_{\bar{x}}$[2]	Percentage of control	$\bar{x} \pm ts_{\bar{x}}$	Percentage of control	$\bar{x} \pm ts_{\bar{x}}$	Percentage of control
7 weeks (70 g)	Controls	6	46 3 ± 20 4	100	38 4 ± 17 1	100	35 4 ± 18 7	100
	$BaSO_4$ II (3 8)	6	36 2 ± 9 2	n s[3]	29 8 ± 2 7	n s	28 9 ± 8 0	n s
20 weeks (210—225 g)	Controls	6	50 2 ± 15 4	n s	34 2 ± 18 8	n s	26 4 ± 15 7	n s
	$BaSO_4$ II (3 8)	6	31 7 ± 17 0	n s	20 4 ± 9 6	n s	14 5 ± 8 4	n s.
10 weeks (100 g)	Controls	6	47 3 ± 0 6	100	36 8 ± 6 2	100	29 1 ± 5 4	100
	$BaSO_4$ III + Na_2SO_4 (8 9)	6	29 2 ± 1 1	62	13 3 ± 5 7	36	10 1 ± 4 8	35
16 weeks (180—185 g)	Controls	6	41 0 ± 1 6	100	31 3 ± 12 4	100	26 6 ± 9 4	100
	$BaSO_4$ III + Na_2SO_4 (8 9)	6	20 8 ± 1 0	51	9 5 ± 5 2	30	6 3 ± 3 5	24
7 weeks (70—80 g)	Controls	6	68 7 ± 9 9	100	52 4 ± 7 6	100	47 6 ± 5 6	100
	$BaSO_4$ III + Na_2SO_4 (7 6)	6	18 8 ± 5 1	27	11 0 ± 2 2	21	10 5 ± 3 0	2?
20 weeks (210—220 g)	Controls	6	45 0 ± 17 0	100	30 0 ± 9 6	100	26 1 ± 8 9	100
	$BaSO_4$ III + Na_2SO_4 (7 6)	6	33 5 ± 9 6	74	7 1 ± 2 9	24	5 1 ± 2 3	20

[1] Content of ⁸⁵Sr in 1 femur × 20

[2] Arithmetic mean ± standard error of the mean multiplied by t value for 95 confidence level

[3] Difference not statistically significant

differed only slightly Skiabaryum with sodium sulphate was the least effective of all the combinations tested in vitro and in vivo We assume a disturbing influence of other ingredients in Skiabaryum to be the cause but this could not be confirmed in the experiments

Many authors pay attention to the influence of a stable isotopic carrier

administration of a standard rat diet (0 75 g in 2 ml distilled water per dose) decreased under these conditions the skeletal retention of ⁸⁵Sr by 30 % in comparison with the controls *On the other hand*, according to JONES (1955) the fact that rats were fasting up to 24 hours before the administration of radiostrontium did not influence its retention When rats fasted even after that the absorption doubled TAYLOR et coll (1962) reported that in starved as well as fed rats 6 to 8 weeks of age, the same amount of ⁸⁵Sr was observed whereas in older animals (60 to 70 weeks of age) which had been starved for 18 hours before the administration of radiostrontium its absorption increased significantly (by 50 % 7 hours after the administration) Finally BRUCE (1963) confirmed the results of MACDONALD et coll (1955) and stated that the retention of radiostrontium decreased threefold when stock diet containing 50 % bone meal was fed immediately after the dose of radiostrontium

In the present experiments the ⁸⁵Sr was administered regularly in the morning It is probable owing to the daily cycles in rats that the intestines were filled at the moment of ⁸⁵Sr administration when fed ad lib The fasting animals in one of the experiments were fed with several grams of food immediately before the Sr was administered

The animals in the present experiments absorbed two and a half times more ⁸⁵Sr when fasting than after feeding on a standard laboratory diet which is in agreement with results obtained by the previously mentioned authors The unusually high radiostrontium absorption from the digestive tract observed in a previous clinical study in fasting human subjects could also be explained in this way (VOLF 1963) There is actually no discrepancy with other published data according to which there was much less absorption after the administration of radiostrontium with breakfast Two cases of accidental ⁹⁰Sr inhalation in fasting man after several hours of work (VOLF 1961) are recalled The degree of radiostrontium absorption might of course in other cases be influenced by the presence of food in the intestine

An important conclusion may therefore be drawn that while after the administration of barium sulphate alone there was no difference between the treated rats and the fed controls a significant difference appeared after the administration of the same preparation I of barium sulphate combined with sodium sulphate The skeletal retention of ⁸⁵Sr then decreased after treatment to approximately the same level in fasting as in the other animals This means that a sufficiently effective substance might cause a decrease in the intestinal radiostrontium absorption in the presence of various food components furthermore less effective means might influence the result to a hardly greater extent than the food alone

It is known that radiostrontium accumulates in the bones of young growing

HARRISON et coll. (1957) considered that the amount of radiostrontium absorbed from the alimentary canal after a *single dose is approximately* proportional to the dose. However, there is a relatively small effect on the retention of an oral dose of radiostrontium because the rate of its urinary excretion increases at the same time, this increase indicates the progression within the range of 2 to 100 μg carrier strontium per gram bodyweight. KAWIN (1959) administered radiostrontium together with increasing doses of stable strontium (0 to 1 263 μg Sr^{2+}) per gram bodyweight. After the oral administration and sufficiently high carrier doses the retention of radiostrontium increased towards, but did not exceed, values obtained following intraperitoneal injection.

The present authors administered 10 μg Sr^{2+} (per 200 gram bodyweight), i.e. approximately 1.5 μg/gram bodyweight. There was also a tenfold addition of carrier with barium sulphate, in amount that, according to HARRISON et coll. (1957) and KAWIN (1959), may influence the absorption and elimination of radiostrontium but not its skeletal retention. BERAK (1963), when investigating the influence of various ions on the ability of barium sulphate to bind radiostrontium in vitro, obtained the lowest percentage of sorption in preparations contaminated by Sr^{2+}.

The carrier added to ^{85}Sr could consequently, in the presence of sulphates lead to an undesirable effect, especially in the case of barium sulphate where the retention of ^{85}Sr tends to increase with the carrier. It is also possible that ^{85}Sr in the presence of a carrier is adsorbed to a smaller extent on the gastric mucosa and passes to the small intestine where it is better absorbed than carrier free ^{85}Sr *and the possibility of its binding by sulphate is thus decreased.*

Fasting animals were often used when attempts were made to influence the intestinal absorption of radiostrontium. The aim was to exclude the effect of a complex of known and unknown factors upon the intestine during the digestion of food. These factors include surface adsorption, the forming of soluble or insoluble complexes, ion exchange etc.

It was apparent from CRAMER's experiments (*1959*) that previous *feeding* increased the emptying of stomach and the movement of radiostrontium through the duodenum and jejunum but resulted in longer retention in the ileum. The emptying of the colon also occurred earlier.

Other authors also observed the difference between the radiostrontium retention in feeding and fasting animals. COPP & GREENBERG (1944) report that the absorption in rats, fasting for two days prior to, or following the administration of, strontium increased.

MACDONALD et coll. (1955) administered foods with varying calcium and phosphorus levels immediately after an oral dose of ^{90}Sr to fasting rats. The

SUMMARY

The average effect of various barium sulphates differed substantially but always increased considerably in the presence of soluble sulphates. The action of sulphates was only slightly influenced by carrier strontium. Barium sulphate in fed animals decreased the retention of Sr only in combination with sodium sulphate.

ZUSAMMENFASSUNG

Die durchschnittliche Wirksamkeit verschiedener Bariumsulfate schwankte beträchtlich aber sie zeigte sich immer stark vergrössert wenn lösliche Sulfate anwesend waren. Die Aktivität der Sulfate war nur begrenzt abhängig von der Anwesenheit von Trägerstrontium. Die Fütterung von Versuchstieren mit Bariumsulfat verminderte die Retention von Sr lediglich in Kombination mit Sodiumsulfat.

RÉSUMÉ

L'effet moyen de divers sulfates de baryum sur la rétention de Sr chez des rats diffère de façon importante mais augmente toujours considérablement en présence de sulfates solubles. L'action des sulfates n'est que légèrement influencée par le strontium non radioactif. Chez les animaux qui ont mangé le sulfate de baryum ne diminue la rétention de Sr que s'il est associé à du sulfate de sodium.

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animals at a higher rate and in greater amounts than in adults. It may be expected that the response to various interferences with the radiostrontium metabolism will also depend on the age of the experimental animal.

WASSERMAN & COMAR (1960) assumed that the effectiveness of dietary calcium in reducing radiostrontium retention may be influenced mainly by the maturity of the animal, apart from the calcium phosphorus ratio of the diet. In immature rats, elevated dietary calcium levels reduce the body burden of dietary radiostrontium almost proportionally, while in adult rats it is necessary to increase the dietary calcium and phosphorus simultaneously and *still the final effect is less marked*.

LINIECKI et coll. (1962) also observed that a high strontium diet substantially reduced known differences in the retention of intravenously injected ^{90}Sr in animals of various ages. The whole body retention of ^{90}Sr (80 days after injection) was in comparison with controls five times lower in the group of youngest rats (1 1/2 months of age,) three times lower in the older (7 1/2 months of age), and twice as low in the oldest rats (13 1/2 months of age). MICHON & GOULLOUX (1958), however, observed in short term experiments, in which radiostrontium was administered in a single dose, that the ion exchangers minimized its intestinal absorption more in adult than in young rats.

The retention of ^{85}Sr in the present experiments was lower in adults than in the young rats in which sulphates were administered in the same quantity per unit of bodyweight. However, when comparing the treated animals with the respective controls, it seems that there is only a slight difference in the relative decrease of ^{85}Sr retention in animals of various ages. In other words it is possible with treatment performed in time to reduce the intestinal radiostrontium absorption to approximately the same extent in young as in adult animals. It must nevertheless be remembered that the final radiostrontium retention will be substantially higher in younger than in older individuals.

Finally the possibility of simple practical applications of the results achieved was investigated with natural mineral waters. 'Zaječická hořká' is a pure bitter mineral water and contains about two and a half times more magnesium ions than sodium ions. 'Šaratica' is on the other hand a concentrated saline bitter mineral water, containing three times more sodium ions than magnesium ions. The total content of sulphate ions is the same in both mineral waters.

The effect of bitter mineral waters and their combination with barium sulphate did not differ in principle from results achieved after the administration of various sulphates and their combinations.

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FROM THE DEPARTMENT OF RADIATION THERAPY TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL PHILADELPHIA, U S A

EFFECTS OF DIFFERENT PARAMETERS ON DOSE DISTRIBUTIONS IN COBALT 60 PLANAR ROTATION

by

K C TSIEN J R CUNNINGHAM and D J WRIGHT

The problems involved in making a comparative study of moving field dose distributions are well known The foremost of these is the need for a large number of comparable dose distribution data with different values of para meters such as field sizes degrees of rotation sizes and shapes of phantom etc Because the calculations (or measurements) involved in determining moving field dose distributions are tedious several earlier works developed approximate methods of calculation but the procedures were still too time consuming to obtain a large number of dose distributions Another problem has been that in most cases the results obtained by different methods of calculation cannot be used in a comparative study owing to the different assumptions being introduc ed into them The development of the use of digital computers in the calculation of moving field distributions (4 9 15, 16 18 20 21 22 24, 25 27) has removed these problems and the effects of different physical and geometrical parameters on dose distributions can now be studied more completely

The present study of the effects of different parameters in planar rotation of cobalt 60 beams is based on part of the findings in a project on the study of

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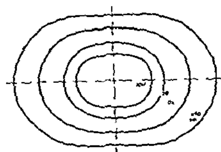


Fig 1 Different sizes of oval phantom according to HAYNES and FROESE's equation

ray of the beam describing a plane perpendicular to the long axis of the patient a motion which is also known as circumaxial moving beam (7) Other moving beam techniques such as bi arc and bi centric planar rotation or conical rotation are not included In this study the three parameters indicated by an asterisk (*) in the above list remained unchanged The effects of the other parameters studied in this paper are based on dose distributions from measured single field isodose curves for a cobalt 60 beam of a 2 cm diameter source at 33 cm from the distal end of the collimator and 75 cm from the center of rotation The values of field sizes degrees of rotation, and shapes and sizes of body contour (idealized) used in this study were as follows

1 *Field sizes*
Geometrical definition at the center of rotation
4 × 4 cm   6 × 6 cm   8 × 8 cm
10 × 10 cm   12 × 12 cm   15 × 15 cm

2 *Degrees of rotation*
360 300 240° 180 and 120

3 *Shapes and sizes of phantom*
Circular 10 cm 20 cm 30 cm and 40 cm diameter
Oval (see Fig 1)
10 × 15 cm   15 × 20 cm   20 × 30 cm   25 × 40 cm

HAYNES and FROESE's (1957) equation of idealized body contour is

$$r = A - B \cos 2\theta$$

where $A = (a + b)/2$, $B = (a - b)/2$, a and b are the semi major and semi minor axes of the phantom

In calculation of dose distributions the tissue dose at the centre of rotation was always taken as 100 The advantages of this are that the dose at a definite point is taken as the reference thus excluding any possible ambiguity and

radiation dose distributions sponsored by the International Atomic Energy Agency (23). The calculations were carried out at the Institute of Computer Science of the University of Toronto using an IBM 7090 computer. The details of the method of calculation will be described elsewhere.

Studies on the effects of different parameters to moving field dose distributions in general follow one of two different approaches. One approach is to take the so called 'efficiency of therapy' defined either as the ratio of the maximum skin dose to the dose at the target center (17), or as the ratio of the integral dose in the target volume to the total integral dose in the body (5). This latter ratio is also called the 'integral dose efficiency factor' (3). As has been pointed out by FRANK ELLIS, (1959), the integral dose is not of great importance as long as it remains below a level between 25 and 30 megagram rad. The homogeneity of dosage throughout the tumour, the avoidance of 'hot spots' and the dose level in the healthy tissue should be of major importance. The second approach is to compare directly the complete dose distribution patterns, and this is the approach adopted in the present study.

Scope of study

Physical and geometrical parameters in moving beam therapy can be considered in three categories: (1) characteristics of the radiation beam, (2) motion of the beam and (3) the characteristics of the irradiated body. The different parameters in each category are as follows:

1. *Radiation beam*
   Energy of the radiation*
   Field size
   Dose distributions of single stationary beam (penumbra and shape of isodose curves)

2. *Motion*
   Type of motion*
   Distance from the source to the centre of rotation, SAD

3. *Irradiated body*
   Shape and size of the body
   Position of the centre of rotation in the irradiated body
   Composition of body material*

This paper is limited to a study of cobalt 60 dose distributions in homogeneous unit density phantoms using simple planar rotation, i.e. with the central

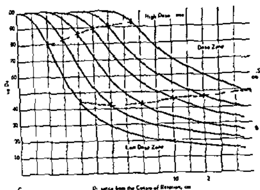


Fig 2 Dose profiles on a radius of a 30 cm diameter circular phantom with field sizes 4 × 4 6×6 8 × 8 10 × 10 12×12 and 15 × 15 cm of cobalt 60 360 degree rotation

I Center of rotation at center of phantom, 360 degree rotation

The dose distributions of 360 degree rotation with the center of rotation at the center of a circular phantom are simplest and the isodose curves in such cases are a series of circles with a common centre at the centre of rotation As long as the phantom remains circular, a change in the values of various parameters such as field size size of the phantom etc will affect only the length of radii of the isodose circles and therefore comparison of different dose distributions may be made by simple comparing of the lengths of radii of different percentage isodose circles When the phantom is oval in shape, the isodose curves are also oval but with their long axes at right angles to the major axis of the oval phantom However the oval pattern is less prominent for the high percentage isodose curves than for the lower ones The 90 % and 80 % isodose curves for instance are generally very nearly circles

A *Effect of field size in the plane of rotation* As has been pointed out by several investigators (11 12 13 26) the length of the field perpendicular to the plane of rotation has little effect on the dose distribution in the plane of rotation Only the field width in the plane of rotation is important Our findings also confirmed this conclusion In practice the dose distribution in the plane of rotation for any square field can be equally used for other field sizes so long as the field width in the plane of rotation remains the same The increase of field width in the plane of rotation has two important effects on dose distributions (1) the area of the continuously irradiated region is increased and (2) the doses at points outside the continuously irradiated region become higher

The effect of the field size on dose distributions may be first considered by noting the variation of doses on any radius of a circular phantom with 360 degree rotation

Table 1

Distances in cm from center of 360 degree rotation to various percentage isodose curves in a 30 cm diameter circular phantom with six different field sizes, and ratios of these distances to the half field widths

% Dose	Field sizes in centimeters					
	4 × 4	6 × 6	8 × 8	10 × 10	12 × 12	15 × 15
	Distance from center of rotation					
100	0	0	0	0	0	0
90	1.4	2.5	3.7	4.9	6.1	7.7
80	2.0	3.2	4.5	5.7	6.9	8.7
70	2.5	3.7	5.2	6.5	7.9	10.0
60	3.0	4.4	5.9	7.5	9.2	11.9
50	3.6	5.2	6.9	9.0	11.2	14.6
40	4.4	6.3	8.6	11.7	14.5	—
30	5.8	8.7	12.0	—	—	—
20	9.4	—	—	—	—	—
	Ratio of distance to half field width					
90	0.75	0.83	0.93	0.98	1.02	1.03
80	1.00	1.07	1.12	1.14	1.15	1.16
60	1.50	1.46	1.48	1.50	1.53	1.59
50	1.80	1.73	1.73	1.80	1.87	1.95

further that the isodose curve is then tied to the only point where a dose calculation can be carried out simply from a knowledge of the patient's contour and tabled quantities, such as tissue air ratios It may be noted, however, that as a result, in the cases of arc rotation or in cases when the centre of rotation is not at the geometrical centre of the idealized phantom (eccentric set up), the maximum doses in the calculated dose distributions have values higher than 100, and will no longer always be at the centre of rotation

The analyses of data are presented in four sections as below

I Center of rotation at center of the phantom 360 degree rotation

II Center of rotation at center of the phantom, arc rotation

III Center of rotation not at center of the phantom, 360 degree and arc rotation

(In addition, dose distributions of a cobalt 60 beam under other geometrical conditions were also calculated, and they are discussed in a further section)

IV Comparison of dose distributions for beams with different sizes of penumbra and at different source axis distances

Table 2

Distances in cm from center of 360 degree rotation to various percentage isodose curves on both major and minor axes of a 20 × 30 cm oval phantom with six different field sizes

Dose	Field sizes in centimeters								
	4 × 4			6 × 6			8 × 8		
	Minor	Major	Diff	Minor	Major	Diff	Minor	Major	Diff
100	0	0	0	0	0	0	0	0	0
90	1 5	1 4	0 1	2 6	2 4	0 2	3 9	3 5	0 4
80	2 1	1 9	0 2	3 3	3 0	0 3	4 6	4 2	0 4
70	2 6	2 3	0 3	4 0	3 6	0 4	5 4	4 9	0 5
60	3 1	2 8	0 3	4 7	4 2	0 5	6 3	5 6	0 7
50	3 8	3 4	0 4	5 6	4 9	0 7	7 4	6 4	1 0
40	4 9	4 0	0 9	7 0	5 8	1 2	9 3	7 7	1 6
30	6 6	5 2	1 4	9 5	7 5	2 0	—	10 3	—
20	—	7 9	—	—	13 0	—			

Dose	10 × 10			12 × 12			15 × 15		
	Minor	Major	Diff	Minor	Major	Diff	Minor	Major	Diff
100	0	0	0	0	0	0	0	0	0
90	5 1	4 7	0 4	6 3	5 9	0 4	8 0	7 4	0 6
80	6 0	5 5	0 5	7 2	6 6	0 6	9 0	8 4	0 6
70	6 9	6 2	0 7	8 3	7 5	0 8	—	9 3	—
60	8 0	7 0	1 0	9 6	8 6	1 0	—	10 9	—
50	9 6	8 3	1 3	—	10 1	—	—	13 3	—
40	—	10 3	—	—	12 7	—			
30	—	14 0	—						

other hand the ratio for 50 % dose increases faster for field widths larger than 10 cm From these results we may draw the conclusion that when the field width is over 10 cm the increase of the area of 100—90 % high doses with the field width becomes more gradual as compared with the increase of area with doses in the range of 90—50 %

Similar data for a 20 × 30 cm oval phantom are given in Table 2 Irrespective of the field width the distance from the centre to any isodose curves on the minor axis is always greater than the corresponding distance on the major axis of the phantom As the field width is increased the difference between the distances on the two axes also increases and this difference is more marked for the lower percentage isodose curves

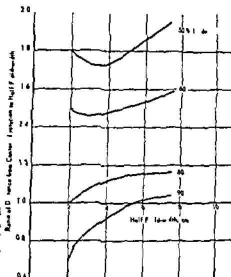


Fig 3 Ratio of distances between center of rotation and the 90 % 80 % 60 % and 50 % isodose curves to corresponding half field width plotted against the half field width 360 degree rotation with a 30 cm diameter circular phantom

The distances from the centre of rotation to various percentage isodose curves for a 30 cm circular phantom with field sizes 4 × 4 cm, 6 × 6 cm, 8 × 8 cm, 10 × 10 cm, 12 × 12 cm and 15 × 15 cm are given in Table 1 A graphical representation of the same data are given in Fig 2 We further marked off the distances corresponding to half of the field width and the full field width from the center of rotation on each curve in Fig 2, and joined each series by a dotted line The upper dotted line shows the variation of dose at the edge of different geometrical widths of the field The dose at this position is smaller for smaller field widths (14) It is 80 % for a field width of 4 cm, and 93 % for a field width of 15 cm The lower dotted line in Fig 2 shows the variation of dose at distances equal to the full length of the field width from the centre, which is in the range of 10 % to 50 % for all field widths Since the dose fall off is most predominant in the region between these two dotted lines, we indicated this as the fall off dose zone and noted that in this zone the change of dose is slower for larger fields

In order to further investigate the effects of field width, the ratio of the distances from 90 %, 80 %, 60 % and 50 % isodose curves to the centre to the corresponding half field width were calculated (second part of Table 1) and plotted in Fig 3 These data show that the ratios for field sizes 4 × 4 cm to 15 × 15 cm vary from 0 70 to 1 03 for the 90 % isodoses from 1 00 to 1 16 for the 80 %, 1 50 to 1 59 for the 60 %, and 1 80 to 1 95 for the 50 % In all cases, the 50 % isodose curves are just within the boundary of twice of the half field width It is shown by Fig 3 that whereas the ratio for the 90 % increases faster when the field width is increased from 4 cm to 10 cm, on the

Table 4

Distances in cm from center of 360 degree rotation to the 90 % 80 and 50 % isodose curves on both major and minor axes in four different sizes of oval phantom with field sizes 6 × 6 cm and 15 × 15 cm

Oval phantom cm	90		80 %		50	
	Minor	Major	Minor	Major	Minor	Major
Field size 6 × 6 cm						
10 × 15	2 5	2 4	3 2	3 1	—	5 0
15 × 20	2 6	2 5	3 2	3 1	5 3	5 0
20 × 30	2 6	2 4	3 3	3 0	5 6	4 9
25 × 40	2 7	2 4	3 4	3 0	5 9	4 7
Max diff	0 2	0 1	0 2	0 1	0 6	0 3
Field size 15 × 15 cm						
15 × 20	—	—	—	—	—	—
20 × 30	8 0	7 4	9 0	8 4	—	13 3
25 × 40	8 4	7 3	9 6	8 3	—	13 0
Max diff	0 4	0 1	0 6	0 1	—	0 3

In the cases of oval phantoms changes in the size of the phantom have only slightly more marked effects for larger field sizes The data in Table 4 show that while for field size 6 × 6 cm the maximum difference between the distances of 90 % or 80 % isodoses to the centre for different phantoms is 2 mm on both the minor and the major axes so is for field size 15 × 15 cm the difference 4 mm between the distances of the 90 % isodoses on the minor axis and 6 mm of the 80 % isodoses The difference between distances of 90 % or 80 % isodoses to the centre on the major axis is in all cases only 1 mm though the difference between the distances of the 50 % isodoses are somewhat larger As the phantom size increases the differences between the distances for all percentage isodose curves on the minor and major axes also increases

Based on these results a composite dose distribution chart for any particular field size can be drawn which would be applicable within a range of different sizes of both circular and oval phantoms In Fig 4 an example is given of such a composite dose distribution chart for a field size 6 × 6 cm In practice this composite chart can be used for all fields with a width 6 cm in the plane of rotation and for 10 to 40 cm diameter circular phantoms and 10 × 15 cm to 25 × 40 cm oval phantoms provided that the centre of rotation is at the geometrical centre of the phantom Although the isodose curves in the composite

Table 3

Distance in cm from center of 360 degree rotation to the 90 %, 80 % and 50 % isodose curves in four different sizes of circular phantom with field sizes 6×6 cm and 15 × 15 cm

Circular phantom diameter cm	F.S. 6 × 6 cm			F.S. 15 × 15 cm		
	90 %	80 %	50 %	90 %	80 %	50 %
10	2.4	3.1	—	—	—	—
20	2.5	3.2	5.2	—	—	—
30	2.5	3.2	5.2	7.8	8.7	—
40	2.[illegible]	3.2	[illegible].2	7.8	8.8	16.3
Max. diff.	0.1	0.1	0	0	0.1	—

If we compare the results for a 20 × 30 cm oval phantom with those for a 30 cm diameter circular phantom, it is seen that for a given field width the distance of the same percentage isodose curve from the centre on the minor axis of the oval phantom is always greater than that for the circular phantom, whereas the corresponding distance on the major axis of the oval phantom is always smaller. The effects of the changes in shape and size of the phantom is further discussed in the following section.

B. *Effect of the shape and size of phantoms.* There have been some references to the effects of the shape and size of the phantom on the dose distribution pattern of moving beam in several papers (2, 19). Some have reported that the size of phantom has little effect on the dose distributions, but without any indication as to the magnitude of the effect. BRAESTRUP & MOONEY (1959), however, have shown that the cobalt 60 isodose distribution curves for a 32 × 16 cm elliptical phantom can be applied to other sizes of phantom, varying from each other by a fixed radial increment in all directions, such as 28 × 42 cm, 24 × 38 cm, 20 × 34 cm and 16 × 30 cm.

In the present study, dose distributions were calculated for eight different phantoms: 10, 20, 30 and 40 cm diameter circular phantoms, and 10 × 15 cm, 15 × 20, 20 × 30 and 25×40 cm oval phantoms. The distances from the centre of rotation to the 90 %, 80 % and 50 % isodose curves for field sizes 6 × 6 cm and 15 × 15 cm with 360 degree rotation for the shapes and sizes of phantoms mentioned above are given in Tables 3 and 4. It may be seen from Table 3 that irrespective of the field size, the change in the distance of the 90 % and 80 % isodose curves to the centre does not exceed 1 mm when the diameter of the circular phantom is increased from 10 to 40 cm.

Table 4

Distances in cm from center of 360 degree rotation to the 90 80% and 50 % isodose curves on both major and minor axes in four different si es of oval phantom u ith field si es 6 × 6 cm and 15 × 15 cm

Oval phantom cm	90		80		0	
	Minor	Major	Minor	Major	Minor	Major
Field si e 6 × 6 cm						
10 × 15	2 5	2 4	3 2	3 1	—	5 0
15 × 20	2 6	2 5	3 2	3 1	5 3	5 0
20 × 30	2 6	2 4	3 3	3 0	5 6	4 9
25 × 40	2 7	2 4	3 4	3 0	5 9	4 7
Max diff	0 2	0 1	0 2	0 1	0 6	0 3
Field s e 15 × 15 cm						
15 × 20	—	—	—	—	—	—
20 × 30	8 0	7 4	9 0	8 4	—	13 3
25 × 40	8 4	7 3	9 6	8 3	—	13 0
Max diff	0 4	0 1	0 6	0 1	—	0 3

In the cases of oval phantoms, changes in the size of the phantom have only slightly more marked effects for larger field sizes The data in Table 4 show that while for field size 6 × 6 cm the maximum difference between the distances of 90 % or 80 % isodoses to the centre for different phantoms is 2 mm on both the minor and the major axes so is for field size 15 × 15 cm the difference 4 mm between the distances of the 90 % isodoses on the minor axis and 6 mm of the 80 % isodoses The difference between distances of 90 % or 80 % isodoses to the centre on the major axis is in all cases only 1 mm though the difference between the distances of the 50 % isodoses are somewhat larger As the phantom size increases the differences between the distances for all percentage isodose curves on the minor and major axes also increases

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Table 3

Distance in cm from center of 360 degree rotation to the 90 %, 80 % and 50 % isodose curves in four different sizes of circular phantom with field sizes 6 × 6 cm and 15 × 15 cm

Circular phantom diameter cm	F S 6 × 6 cm			F S 15 × 15 cm		
	90 %	80 %	50 %	90 %	80 %	50 %
10	2.4	3.1	—	—	–	—
20	2.5	3.2	5.2	—	—	—
30	2.5	3.2	5.2	7.8	8.7	–
40	2.5	3.2	5.2	7.8	8.8	16.3
Max diff	0.1	0.1	0	0	0.1	—

If we compare the results for a 20 × 30 cm oval phantom with those for a 30 cm diameter circular phantom, it is seen that for a given field width, the distance of the same percentage isodose curve from the centre on the minor axis of the oval phantom is always greater than that for the circular phantom, whereas the corresponding distance on the major axis of the oval phantom is always smaller. The effects of the changes in shape and size of the phantom is further discussed in the following section.

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Table 4

Distances in cm from center of 360 degree rotation to the 90 80 % and 50 % isodose curves on both major and minor axes in four different sizes of oval phantom with field sizes 6 × 6 cm and 15 × 15 cm

Oval phantom cm	90		80		50 %	
	Minor	Major	Minor	Major	Minor	Major
Field size 6 × 6 cm						
10 × 15	2 5	2 4	3 2	3 1	—	5 0
15 × 20	2 6	2 5	3 [illegible]	3 1	5 3	5 0
20 × 30	2 6	2 4	3 3	3 0	5 6	4 9
25 × 40	2 7	2 4	3 4	3 0	5 9	4 7
Max diff	0 2	0 1	0 2	0 1	0 6	0 3
Field size 15 × 15 cm						
15 × 20	—	—	—	—	—	—
20 × 30	8 0	7 4	9 0	8 4	—	13 3
25 × 40	8 4	7 3	9 6	8 3	—	13 0
Max diff	0 4	0 1	0 6	0 1	—	0 3

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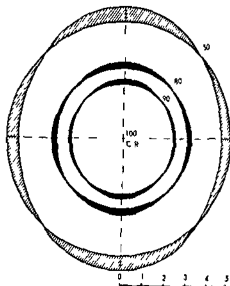


Fig 4 Composite cobalt 60 360 degree rotation dose distribution plan for a field width 6 cm in the plane of rotation (applicable to circular phantoms 10 to 40 cm in diameter and to oval phantoms 10 × 15 cm to 25 × 40 cm in size)

chart are not thin lines, especially the 50 % isodose curves (see Fig 4), this limited uncertainty of the exact position of isodose curves need not hinder its use in treatment planning In fact, in the region of greatest interest, i e near the target, this composite chart is accurate to within 6 mm for all phantom sizes studied

II Center of rotation at center of phantom, arc rotation

The comparison of the effects of different parameters on the dose distribution patterns is more complicated in arc rotation than in 360 degree rotation, mainly because of the introduction of a new variable, i e the arc dimensions Dose distributions for field sizes 4 × 4 cm, 6 × 6 cm 8 × 8 cm, 10 × 10 cm, 12 × 12 cm, and 15 × 15 cm with 300, 240, 180, 120 degrees arc rotation were calculated No attempt is made to reproduce all the data here, since they will appear in an atlas of radiation dose distributions (1) A few selected examples are presented here for the purpose of illustrating some of the effects of certain parameters on the dose distributions However, instead of dealing separately with effects of individual parameters the following sections will discuss in more general terms the changes in the characteristics of dose distributions of arc rotation, with special reference to the magnitude and the position of the maximum dose, the dose profiles on the arc bisecting line, and the shape of isodose curves

A *Magnitude and position of maximum dose* The most distinct feature of dose distributions in arc rotation, irrespective of the shape of the phantom and the

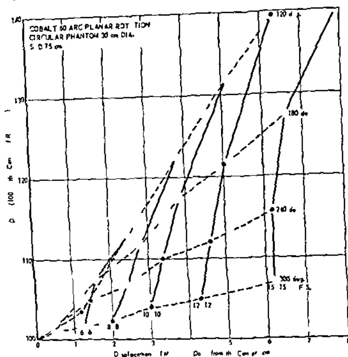


Fig 5 Maximum doses and the displacements from center of rotation of a 30 cm diameter circular phantom for 300 240 180 and 120 degrees of rotation with field sizes 4 × 4 6 × 6 8 × 8 10 × 10 12 × 12 and 15 × 15 cm

field size is the shift of the maximum dose away from the center of rotation This is in contrast to 360 degree rotation where the maximum dose is always at the center of rotation unless the center of rotation is not at the geometrical center of the phantom or the phantom is very irregular in shape

In this study the maximum dose has been calculated always relative to the dose at the center of rotation which is taken as 100 The effect of changes in the degree of rotation is illustrated by plotting the magnitudes of the relative maximum doses and their displacements from the center of rotation as a function of the field width and the degree of rotation as in Fig 5 which is for a 30 cm diameter circular phantom This interesting lattice pattern provides an overall picture of the effects of both the field size and the angle of rotation Taking a special case it is seen that for a field width of 12 cm and 120 degree angle of rotation the relative maximum dose is nearly 40 % higher than the dose at the center of rotation and is displaced about 6 cm away from the center From this graph it is seen that in general the magnitude of the relative maxi

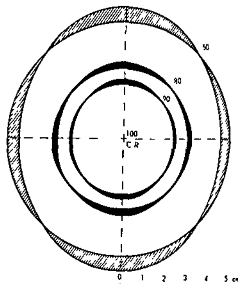


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The comparison of the effects of different parameters on the dose distribution patterns is more complicated in arc rotation than in 360 degree rotation, mainly because of the introduction of a new variable, i e the arc dimensions Dose distributions for field sizes 4 × 4 cm, 6 × 6 cm, 8 × 8 cm, 10 × 10 cm, 12 × 12 cm, and 15 × 15 cm with 300, 240 180, 120 degrees arc rotation were calculated No attempt is made to reproduce all the data here, since they will appear in an atlas of radiation dose distributions (1) A few selected examples are presented here for the purpose of illustrating some of the effects of certain parameters on the dose distributions However, instead of dealing separately with effects of individual parameters, the following sections will discuss in more general terms the changes in the characteristics of dose distributions of arc rotation, with special reference to the magnitude and the position of the maximum dose, the dose profiles on the arc bisecting line, and the shape of isodose curves

A *Magnitude and position of maximum dose* The most distinct feature of dose distributions in arc rotation, irrespective of the shape of the phantom and the

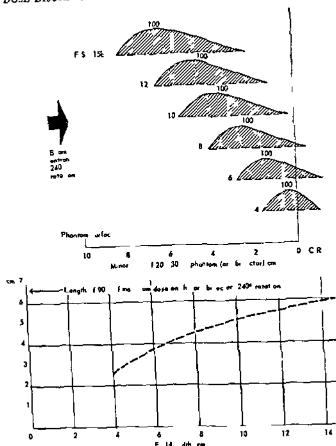


Fig 7 *Upp dia am* Dose profiles (90 of maximum dose portion) of 240 degree rotation on the m nor axis of a 20 × 30 cm oval phantom *Lower d agram* Length of the 90 of maximum do e on the n nor axis of a 20 × 30 cm o al phantom plotted against the field w dth

in that region is less uniform For this reason small angles of rotation are not advantageous for practical purposes

If we take the maximum dose on the dose profiles as 100 % the dotted horizontal lines in Fig 6 indicate the positions where the dose is 90 % of the maximum dose for different field widths The length of the dotted line for each field width thus represents the size of the actual 90 % dose region along the minor axis of the phantom The changes of the length of the 90 % dose region and its position on the minor axis (arc bisecting line) with the field width can be seen more clearly in the upper diagram of Fig 7, where the

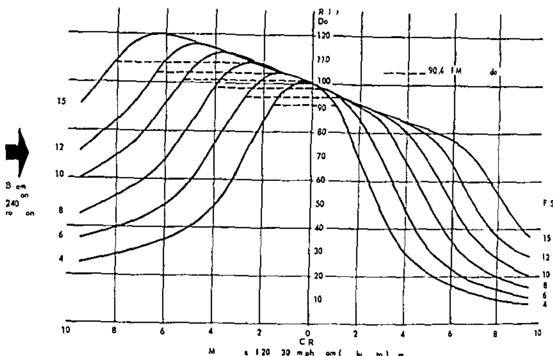


Fig 6 Dose profiles of 240 degree rotation on the minor axis of a 20 × 30 cm oval phantom with field sizes 4 × 4 6 × 6 8 × 8 10 × 10 12 × 12 and 15 × 15 cm

mum dose and its displacement from the center increases with the increase of the field size and with the decrease in the degree of rotation The maximum dose relative to the dose at the center of rotation is higher and further away from the center of rotation for the same degree of arc when the field width is larger, this is also the case when the field width is constant but the angle of rotation is smaller It may also be noted in passing that a graph such as Fig 5 can also be used to estimate the relative maximum dose for other field widths and degrees of rotation within the range given in the graph

B *Dose profiles on the arc bisecting line* The curves in Fig 6 give one example of dose profiles on the arc bisecting line in arc rotation The data are for 240 degree rotation on the minor axis of a 20 × 30 cm oval phantom and six field sizes from 4 × 4 cm to 15 × 15 cm It is seen that while the magnitude of the relative maximum dose increases with larger field widths, as mentioned in the last section the gradient at the central portion of the dose profiles remains constant irrespective of the field width It has been found that the dose profiles on the arc bisecting line for other degrees of rotation also show this same characteristics, but the smaller the arc of rotation the steeper the dose gradient in the central portion of the dose profiles, showing that the dose distribution

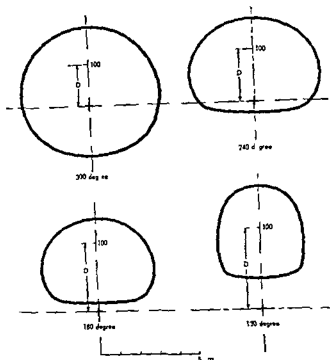


Fig 9 Position and shape of 90 % isodose curves (maximum dose as 100) for a field size 8 × 8 cm with 300 240 180 and 120 degrees of rotation and with a 20 × 30 cm oval phantom taking the minor axis as the arc bisector

But when the degree of rotation is 180 degrees or less the change in the shape of 50 % isodose curves are in the opposite direction, and the lower portion of the curves is convex downwards as shown in Fig 8

Taking the maximum dose as 100 % the positions and shapes of 90 % isodose curves for 300, 240 180 and 120 degrees of rotation are shown in Fig 9 It is seen that with the decrease in the angle of rotation the area enclosed by the 90 % (of maximum dose) isodose curves becomes smaller and more oblong in shape and moves away from the center of rotation

III Center of rotation not at center of phantom (eccentric rotation) 360 degree and arc rotation

Theoretically the center of rotation may be located anywhere in the phantom However discussion in the present paper is limited to cases in which the *center of rotation is always located on the arc bisecting line for arc rotation* and remains on the major or minor axis when an oval phantom is used

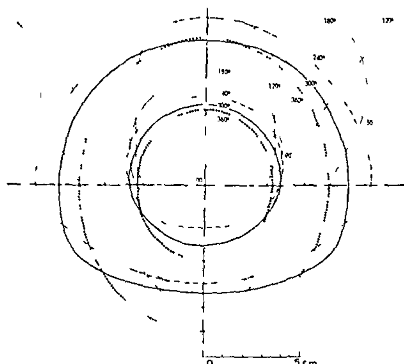


Fig 8 90 % and 50 % isodose curves for a field size 8 × 8 cm with 360 300 240 180 and 120 degrees of rotation and with a 20 × 30 cm oval phantom taking the minor axis as the arc bisector (M indicates the position of the maximum dose)

respective curves for different field widths are no longer superimposed The curve above the 90 % dose dotted line for each field width give indication of the variation of the doses between 90 % and 100 % along this section of the arc bisecting line In the lower diagram of Fig 7, the length of the dotted line is plotted against the respective field width and we see that this length does not proportionally increase with the increase of the field width In fact, the increase becomes relatively small when the field width increases above 8 cm

C *Shape of isodose curves* In arc rotation the shapes of different percentage isodose curves are distinctly different and change with the degree of rotation The 90 % and 50 % isodose curves are shown in Fig 8 for 360, 300, 240, 180 and 120 degrees arc rotation, with a field size 8 × 8 cm, by using a 20 × 30 cm oval phantom, taking the minor axis of the phantom as the arc bisecting line

As seen in the case of the 90 % and 50 % isodose curves, when the degree of rotation becomes less than 360 degrees, the isodose curves are deformed in such a way that the lower portion (the side opposite to the beam entrance surface) of the curve becomes flatter with the decrease in the degree of rotation

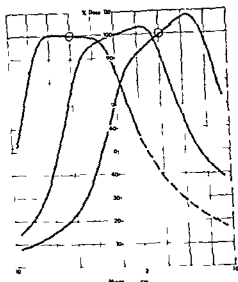


Fig 11 Dose profiles of 300 degree rotation on the arc bisecting minor axis of a 20 × 30 cm oval phantom with field size 8 × 8 cm the center of rotation displaced 4 cm anteriorly and posteriorly from the center of the phantom

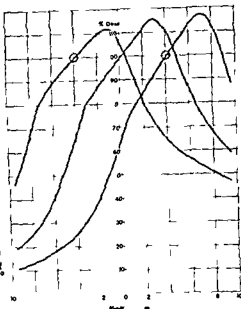


Fig 12 Dose profiles of 180 degree of rotation on the arc bisecting minor axis of a 20 × 30 cm oval phantom with field size 8 × 8 cm the center of rotation displaced 4 cm anteriorly and posteriorly from the center of the phantom

center of rotation is situated on the opposite side of the beam entrance the effect of these two factors on the maximum dose will tend to cancel out each other therefore in some cases of this arrangement a uniform dose distribution is obtained around the center of rotation and the maximum dose is again located at the center of rotation However when the rotation is less than 180 degrees this can not happen because there is no beam entering from the side with less absorbing medium of the phantom

B *Dose profiles on the arc bisecting line* The dose profiles with a field size 8 × 8 cm under three different irradiating conditions are shown in Figs 10 to 12 The dose profiles on the arc bisecting line are given in Fig 10 for 240 degree rotation with a 30 cm diameter circular phantom when the center of rotation is displaced in 2 cm steps on the arc bisecting diameter from the center of the phantom In Fig 11 the dose profiles on the arc bisecting line are given for 300 degree rotation with 20 × 30 cm oval phantom when the center of rotation

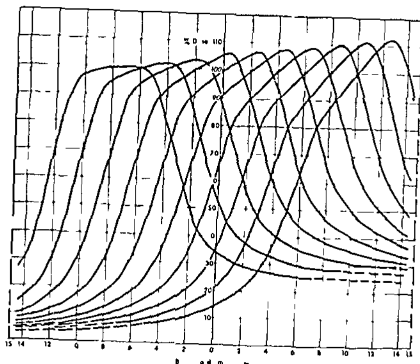


Fig 10 Dose profiles of 240 degree rotation on the arc bisecting diameter of a 30 cm circular phantom with field size 8 × 8 cm the center of rotation displaced 2 4 6 8 10 cm anteriorly and 2 4 6 8 cm posteriorly from the center of the phantom

A *Magnitude and position of the maximum dose* In 360 degree eccentric rotation, the maximum dose is also no longer located at the center of rotation, but moves to the side with less absorbing medium The relative magnitude of the maximum dose and its position depend on how far the center of radiation is away from the geometrical center of the phantom However, it has been found in this study that the magnitude is never too great in comparison with the dose at the center of rotation in all cases with 360 degree rotation

When the angle of rotation is less than 360 degrees whether the center of rotation on the arc bisecting line is situated between the center of the phantom and the entrance side of the beam, or on the opposite side, is also an important factor affecting the dose distribution

When the center of rotation is situated on the arc bisecting line between the the center of the phantom and the entrance side of the beam, the relative maximum dose is generally greater than that obtained with the center of rotation at the center of the phantom The two factors, the arc rotation and the difference of the lengths of absorbing medium in different directions of beam entrance increase the effect on the maximum dose On the other hand, when the

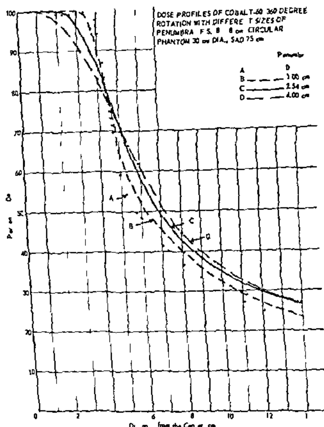


Fig 14 Dose profiles of 360 degree rotation on a radius of a 30 cm diameter circular phantom for field size 8 × 8 cm of cobalt 60 beams with different size of penumbra at a source axis distance 75 cm

profiles on the arc bisecting line change both when the degree of rotation is changed and when the center of rotation is displaced The shapes of the 90 % *and 50 % isodose curves with a field size 8 × 8* cm are shown in Fig 13 for 360 300 240 180 and 120 degree rotation using a 20 × 30 cm oval phantom with the center of rotation displaced 4 cm away from the center of the phantom on the minor axis towards the entrance side of the beam If we compare this diagram with Fig 8 in which case *the center of rotation was at the center* of the phantom it is seen that in spite of a difference of 4 cm between the positions of the center of rotation the general pattern of isodose curves in these two cases for the various degrees of rotation remains the same

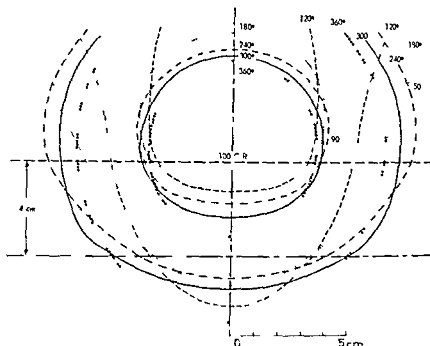


Fig. 13. 90% and 50% isodose curves for field size 8 × 8 cm with 360, 300, 240, 180 and 120 degrees of rotation and with center of rotation displaced 4 cm anteriorly from center of phantom on the minor axis of a 20 × 30 cm oval phantom (minor axis as the arc bisector).

is displaced along the minor axis (arc bisecting line) of the phantom 4 cm to either side of the center of phantom. In Fig. 12, the dose profiles under the same conditions as in Fig. 11, but for 180 degree of rotation, are given.

In Fig. 10, when the center of rotation is displaced 8 cm from the center of the phantom on the side opposite to the beam entrance for 240 degree of rotation, and in Fig. 11, when the center of rotation is displaced 4 cm also on the side opposite to the beam entrance for 300 degree of rotation, the central part of the dose profiles in both cases is nearly flat, which shows that the doses are uniform in that region. From these results it can be seen that a treatment arrangement, by placing the center of rotation between the center of the phantom and the side opposite to the beam entrance on the arc bisecting line, can be a very useful technique with arc rotation. In fact the use of this technique has been suggested by HALE (8) several years ago. However, the use of this technique, presently called "reverse arc technique", cannot possibly have this advantage if the angle of rotation is less than 180 degrees.

C. *Shape of isodose curves.* From the foregoing discussion we have seen that the relative magnitude and the position of the maximum dose, and the dose

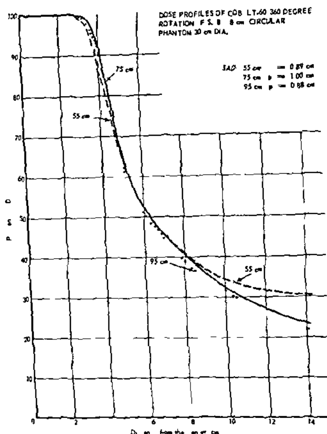


Fig 15 Dose profiles of 360 degree rotation on a radius of a 30 cm diameter circular phantom for field size 8 × 8 cm of cobalt 60 beams with approximate 1 00 cm penumbra at source axis distances 55 cm 75 cm and 95 cm

center of rotation to the 90 % 80 % and 50 % isodose curves for beams with penumbra between 1 and 2 5 cm is not of great importance in the cases at 75 cm SAD

In Fig 15 the dose profiles for beams with penumbra 0 89 cm at SAD 55 cm 1 cm at SAD 75 cm and 0 88 cm at SAD 95 cm are shown It is seen that the dose profiles of these three beams are nearly the same except at the region approaching the surface where the doses with SAD 55 cm are a little higher than others However the differences of dose profiles for a beam with penumbra 2 63 cm at SAD 55 cm and 2 54 cm at SAD 75 cm, are greater, as shown in Fig 16

Table 5

Distances in cm from center of 360 degree rotation to the 90 %, 80 % and 50 % isodose curves in a 30 cm diameter circular phantom with a field size 8 × 8 cm of four different cobalt 60 beams

Type of beam SAD 75 cm			Distance from center of rotation in cm		
Source diameter cm	SDD cm	Penumbra at 75 cm	90 %	80 %	50 %
Hypothetical point source	—	0	4 2	4 5	5 8
2 0	50	1 00	4 1	4 5	6 3
2 0	33	2 54	3 7	4 5	6 9
2 0	25	4 00	3 2	4 3	7 2

IV Comparison of dose distributions for beams with different sizes of penumbra and at different source axis distances

The effects of the size of the penumbra of the beam on dose distributions in plan ir rotation were studied by comparing three sets of data, all for 360 degree of rotation with a 30 cm diameter circular phantom The three sets of data used in this study are as follows (1) dose distributions of four beams with different geometrical sizes of penumbra i e zero (point source), 1 00 cm, 2 54 cm, and 4 00 cm, at SAD 75 cm, (2) dose distributions of three beams, each with approximately the same size of penumbra 1 cm, at SAD 55 cm, 75 cm, and 95 cm, (3) dose distributions of two beams with approximately the same size of penumbra 2 5 cm, at SAD 55 cm and 75 cm The isodose curves used in the calculation for the beams with zero and 4 cm penumbra at SAD 75 cm are hypothetical

Using the first set of data, the dose profiles for a field size 8 × 8 cm are shown in Fig 14 The distances from the center of rotation to the 90 %, 80 % and 50 % isodose curves in these four cases are set out in Table 5 It can be seen that the distance from the center of rotation to the 90 % isodose curve decreases from 4 2 cm to 3 2 cm with the increase in size of penumbra The distance to the 80 % isodose curve remains constant at 4 5 cm as the penumbra is increased from 0 to 2 54 cm, but decreases to 4 3 mm for the beam with a hypothetical large penumbra of 4 cm On the other hand, the distance to the 50 % isodose curve increases from 5 8 cm to 7 2 cm when the penumbra of the beam is increased from 0 to 4 cm If we discount the two hypothetical beams with 0 and 4 cm penumbra the magnitude of the change in distances from the

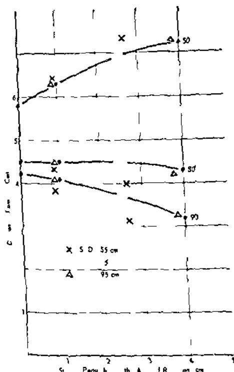


Fig 17 Distances from the center of rotation of a 30 cm diameter circular phantom to the 90 80 and 50 isodose curves with field size 8 × 8 cm plotted against the geometrical size of respective penumbra of cobalt 60 beams at source axis distances 55 cm 75 cm and 95 cm

conclude from these results that the beam with a large penumbra is more undesirable in using rotation techniques with the SAD 55 cm than when the SAD is longer In other words it is more important for a beam to have a smaller penumbra when a short source axis distance is used

Conclusions

The results of the foregoing study of the effects of different parameters on dose distributions in cobalt 60 planar rotation suggest some of the optimum conditions in which the rotation technique may be used to the best advantage in radiotherapy

In the first place full advantage is obtained with the rotation technique only when the field width required in the plan of rotation is not more than 10 cm and when the degree of rotation is larger than 180 degrees This is because with larger field widths the dose fall off outside the constantly irradiated region becomes increasingly less steep and with smaller arcs of rotation the dose in the target volume becomes less uniform Nevertheless, in some cases which necessitate the use of a large field width the use of the rotation technique

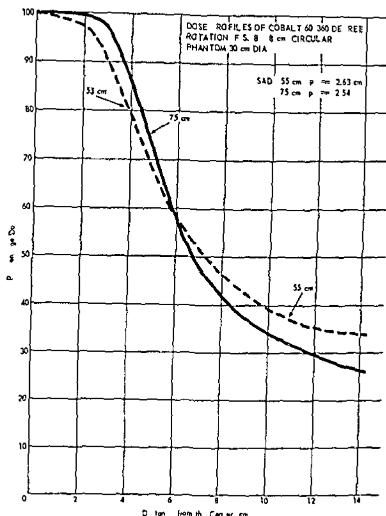


Fig 16 Dose profiles of 360 degree rotation on a radius of a 30 cm diameter circular phantom for field size 8 × 8 cm of cobalt 60 beams with approximate 2 5 cm penumbra at source axis distances 55 cm and 75 cm

Additional information is obtained by plotting the distances from the center of rotation to 90 %, 80 % and 50 % isodose curves against the geometrical sizes of penumbra at the center of rotation with different source axis distances, as shown in Fig 17 This figure gives us an overall picture of the effect of the size of penumbra at different SAD on the dose distributions It shows that there are nearly no differences in the dose distribution for beams with the same penumbra at SAD 75 cm and 95 cm However though the dose distributions for SAD 55 cm show little difference from those for beams at SAD 75 cm and 95 cm, when the penumbra of the beams are all small there is a greater difference as the size of the penumbra is increased, say over 2 cm We may

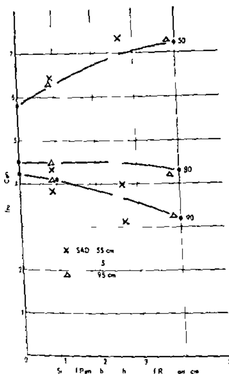


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may be preferred, because the doses received in certain regions outside the target volume is still somewhat less than when using multiple fields On the other hand, cases which might be treated by small arc technique usually can be treated by other methods more adequately, namely by shifting the center of rotation to the center of the target volume, or by using wedge filtered beams

The effect on dose distribution due to the size of body contour was studied in considerable detail with eight different shapes and sizes of phantoms The results obtained not only support previous findings that this effect is not large, but show the magnitude of the displacement of specific isodose curves with changes in the size of body contours It was found that change in the position of the 80 % isodose curve with a field size 15 × 15 cm is of the magnitude of only 6 mm for different sizes of oval phantoms This leads to the conclusion that for practical purposes a composite isodose curve drawn somewhat thicker than usual can be used for a large number of different shapes and sizes of body contours

The results of this study also lead to the conclusion that there is little or no advantage in using a long source axis distance in rotation with cobalt 60 radiation There is no appreciable difference in the dose distributions for rotating beams with the same size of geometrical penumbra either at SAD 75 cm or 95 cm However, a beam with a smaller penumbra is desirable when the rotation is at a SAD 55 cm, when a larger SAD is used, a larger penumbra of the beam is permissible This is because the dose distributions at the SAD 75 cm are relatively insensitive to penumbra changes between 1 and 2 5 cm, while at 55 cm SAD the dose distributions for beams with different sizes of penumbra differ considerably For beams with 1 cm penumbra at both 55 cm and 75 cm SAD, the dose distributions are about the same

From these findings it appears that for any particular cobalt 60 rotating unit, if an atlas of dose distributions, with different field widths, arc of rotation, and positions of the center of rotation in the body, is prepared, then in most routine cases of rotational therapy it would be possible to estimate the positions of the important isodose curves in the body, such as 90 %, 80 % and 50 % curves, within an acceptable degree of accuracy

SUMMARY

The effects of different parameters on dose distributions in cobalt 60 planar rotation were studied with the use of a digital computer The parameters considered were field size angle of rotation position of the center in the phantom shape and size of the phantom and the penumbra of the beam On the basis of the results obtained the conditions under which the rotation technique can be most advantageously used are discussed

ZUSAMMENFASSUNG

Der Effekt verschiedener Parameter auf die Dosis-Distribution in planarer Kobalt 60 Rotationstherapie wurde mit Hilfe eines digitalen Rechenautomaten studiert Die verschiedenen Parameter waren Feldgrosse Rotationswinkel Position des Zentrums im Phantom Form und Grosse des Phantoms und der Penumbra des Strahlenbundels Auf Grund der erhaltenen Resultate wurden die besten Bedingungen bei der Verwendung der Rotationstechnik untersucht

RÉSUMÉ

L effet de divers parametres sur la distribution de dose en cobalt thérapie rotatoire plane a éte étudie au moyen d une calculatrice digitale Les parametres étudiés sont les dimensions du champ l angle de rotation la position du centre de rotation dans le fantome la forme et les dimensions du fantome et la pénombre du faisceau Les auteurs examinent sur la base des resultats obtenus les conditions les plus avantageuses de l emploi de la technique rotatoire

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FROM THE RADIOTHERAPY DEPARTMENT CHURCHILL HOSPITAL OXFORD, ENGLAND

ROUTINE DOSIMETRY WITH TANTALUM 182 AND IRIDIUM 192 WIRES

by

E J HALL R OLIVER and B J SHEPSTONE

For more than ten years flexible radioactive wire has been used for interstitial therapy as an alternative to sealed radium sources

Tantalum 182 wire has been described by SINCLAIR (1952) and its clinical application reported by several workers including WALLACE STAPLETON & TURNER (1952) ELLIS & OLIVER (1954) VAN MIERT & FOWLER (1956) and ALLT & HUNT (1963)

Iridium 192 wire was not introduced until a later date PIERQUIN (1964) described its use pointing out that its lower gamma energy greatly simplifies protection problems The physical properties of tantalum 182 and iridium 192 together with the dimensions of the wires used in this department are summarised in a Table

The purpose of the present communication is to make available our basic data to new users to avoid further duplication of effort

The plan in our department has been to express the activity of the tantalum 182 or iridium 192 wire in terms of mg of radium equivalent per cm filtered by 0 5 mm of platinum This quantity is obtained by comparing a short length

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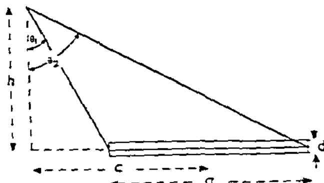


Fig 1 Geometry of dose calculation for linear radioactive wire.

data graphically in a similar way to the data sheets for standard Amersham radium needles calculated by KEMP (1950) and KEMP & HALL (1952) and made available through the International Atomic Energy Agency The calculations were carried out in the following way

The dose rate (in rad per hour in soft tissue) at a point P due to a radioactive line source of length a cm filtered by material of thickness d (mm) is given by the expression below which follows closely that derived originally by SIEVERT (1923 1932)

$$I_p = \frac{8.05\, p f}{h} \int_{\theta_1}^{\theta_2} e^{-\frac{\mu d}{\cos\theta}} d\theta \qquad (1)$$

where

$\theta_1 \quad = \tan^{-1} \frac{c - a/2}{h}$

$\theta_2 \quad = \tan^{-1} \frac{c + a/2}{h}$

h = perpendicular distance of the point P from the wire (cm)

c = the cross line i e the distance from the centre of the wire to the foot of the perpendicular from P (cm)

8.05 = specific gamma ray constant for radium (8.3) × roentgen to rad conversion factor for soft tissue (0.97)

p = measured activity of the wire per cm expressed in equivalent mg of radium filtered by 0.5 mm of platinum

f = correction factor to convert the linear activity of the wire measured through the screenage to true linear activity

μ = linear absorption coefficient of the filtering material i e platinum (mm^{-1})

Table

Comparison of tantalum 182 and iridium 192 wire

Property	Tantalum 182	Iridium 192
Half life	115 days	74 days
% decay per week	4 %	6
Principal gamma energy range	1.1 to 1.2 MeV	0.3 to 0.6 MeV
Specific gamma ray constant cm^2 R/mCi hr	6.8	4.8
Approx. HVL in lead	1 cm	3 mm
Approx. 1/10 value layer in lead	3 cm	1.2 cm
Wire dimension		
O.D.	0.4 mm	0.3 mm
Core	0.2 mm	0.1 mm
Pt. filtration	0.1 mm	0.1 mm
Cost of 100 cm of wire + irradiation for 2 weeks + measurement	£26	£15
Approx. activity produced	1 mCi/cm	1.5 mCi/cm

of the wire against a radium needle of the same active length and a known radium content. The comparison is effected by inserting the wire and needle in turn into a re-entrant ionisation chamber. By always referring to the activity of the radioactive wire in terms of its radium equivalent, the confusion of using several specific gamma ray constants in routine calculations is avoided.

To calculate dose rates from implants with radioactive wire, VAN MIERT & FOWLER (1956) followed the Paterson-Parker system. HAYBITTLE (1957) has considered in detail the dose distribution resulting from hairpins of tantalum 182 wire and discussed the conditions under which the Paterson-Parker tables could be used with reasonable accuracy. In many cases, however, the standard dosage tables cannot be applied to tantalum 182 and iridium 192 wire implants because, in general, wires of different linear activities are not available to implement the distribution rules for moulds and surface applicators. In addition, one of the advantages of wires is that they may be used as long sources, the resulting implants having extremely large elongation ratios. As a result it is often simpler to calculate doses by considering the contributions from individual wires, provided the basic data are available in a convenient form. It was thought necessary therefore to calculate the complete dose distributions around radioactive wires of various lengths, and to present the

wire Copies of such data sheets from these calculations for tantalum 182 and *iridium* 192 wires of lengths from 2 to 15 cm are now available at a nominal charge on application to the Medical Section Department of Research and Isotopes International Atomic Energy Agency, Vienna 1 Kaerntnerring 11, *Austria*

Acknowledgements

The stimulus to develop the work described in this paper came from Dr Frank Ellis Director of the Radiotherapy Department who routinely uses radioactive wire for implants We wish to record our appreciation of the facilities provided for us by Professor L Fox the Director of the Oxford University Computing Laboratory for the computations involved

SUMMARY

Data sheets have been prepared of the dose distribution around radioactive wires of *tantalum* 182 and iridium 192 A computor was programmed to perform the calculations which included an allowance for oblique filtration in the platinum screen

ZUSAMMENFASSUNG

Data Tabellen wurden aufgestellt die die Dosisverteilung radioaktiver Drahte aus Tantal 182 und Iridium 192 geben Eine elektronische Rechenmaschine wurde programmiert um solche Berechnungen auszufuhren wobei eine schrage Filtrierung durch das Platinfilter gesichert wird

RÉSUMÉ

Les auteurs ont établi des tableaux donnant la distribution de dose autour de fils radioactifs de tantale 182 et d iridium 192 Un ordinateur a été programmé pour faire ces calculs qui tiennent compte de la filtration oblique à travers le filtre de platine

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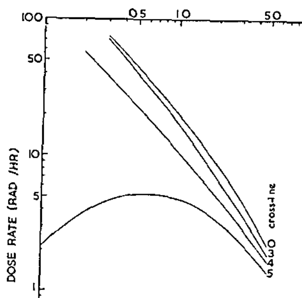


Fig. 2. Data sheet for a length of 8 cm ^{192}Ir wire of activity 1 mg radium equivalent per cm filtered by 0.3 mm of platinum. Distance and cross line are the quantities labelled h and c respectively in fig. 1.

Eq. (1) has been evaluated for tantalum 182 and iridium 192 wires of lengths from 2 to 15 cm. The values of the constants used for the two isotopes are summarized below.

Constant	Tantalum 182	Iridium 192
p	1.0	1.0
f	1.02	1.07
μ (mm^{-1})	0.11	0.43
d mm	0.40	0.30

When calculating the dose distributions due to radium filtered by a platinum screen KeMI (1950, 1952) introduced a screenage function which allows for the fact that since the gamma radiation is not homogeneous, the effective absorption coefficient of the platinum is a function of path length and therefore varies with obliquity. In the present calculations this effect is ignored and assumed to be constant because the platinum sheath is much less thick in the case of radioactive wire than for radium.

The University of Oxford Mercury Computer was programmed to perform the calculations, making use of the standard Sievert integrals available in the library of this machine. The resultant data were plotted graphically. Fig. 2 gives an example of one of the data sheets for a length of 8 cm of iridium 192

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ELECTRON BEAM IRRADIATION OF BRAIN OF RAT AND DOSE MODIFYING EFFECT OF ANOXIA

by

N A SHARPLES and A G JACOBS

The susceptibility of cells to high LET radiation damage is profoundly influenced by the concentration of oxygen present in the cell at the instant after the radiation energy arrives and according to GRAY (1953) both specific lesions and whole body effects can be modified according to the prevailing level of oxygenation From their work on *E coli B*, ALPER & HOWARD FLANDERS (1956) showed that radiosensitivity was maximally affected by environmental oxygen tensions of the range 0 to 10 mm Hg partial pressure, wherein a two- to threefold alteration in radiosensitivity could be obtained This work has been applied to mammalian tissues by WRIGHT & HOWARD FLANDERS (1956) using mouse tails by VAN DEN BRENK et coll (1962) using mouse limbs, and by GRAY et coll (1952) using whole body irradiation

The malignant cell whose oxygen tension is low is able to survive doses of irradiation that would damage or destroy fully oxygenated cells The anoxic radioresistant cell has long troubled radiotherapists because the radiocurability of a tumour depends on being able to prevent all the malignant cells repro

From the Department of Pathology St Mary s Hospital Medical School *London* England

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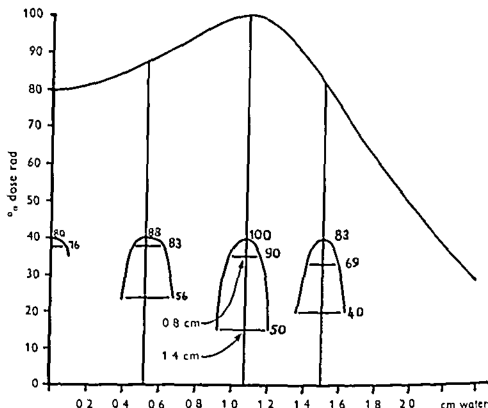


Fig 1 Depth dose data of the electron beam showing rapid fall off at depth

ducing, including any anoxic cells, even though these latter may only amount to 1 % of the total malignant mass Some workers, Churchill Davidson (1957), Emery (1960), have tried to solve the problem by subjecting the whole patient to increased partial pressures of oxygen to try and raise the oxygen content of the tumour prior to, and during, irradiation therapy Apart from the technical problems involved in this form of pre treatment therapy, its effectiveness is directly dependent on the efficiency with which the capillary network of the tumour transports the extra available oxygen to each and every cell in the mass The vascular network on which this mode of therapy relies is often poorly developed Further whilst the rise in oxygen content of the malignant cells is possibly subject to variation, the normal tissue in the area has its radiosensitivity raised to its maximum value, which may result in more damage than can be accepted being suffered by normal structures in the region under treatment An alternative approach is to try and take advantage of the poor vascularity of the tumour, which is the limiting factor to alterations in tissue gas tensions Instead of attempting to raise the oxygen level of tumour and adjacent tissue, it is suggested that the normal tissue has its oxygen tension lowered by de

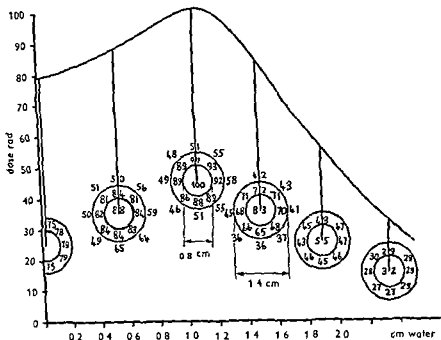


Fig 2 Depth dose data of the electron beam showing fall off from central axis

priving it of its normal supply of oxygen By virtue of its better blood supply the normal tissue can be brought into equilibrium with blood of very low *oxygen content fast r than the abnormal tissue can* so the tissue oxygen con centration of the normal tissue should fall to below that of the tumour tissue, provided that the normal tissue does not contain any reserves of oxygen Thus by reversing the usual oxygen content status the tumour is made relatively *more radiosensitive than its adjacent normal tissue* (WRIGHT 1960)

We have been investigating the possibility of applying such a technique to the only tissue that can quickly be made anoxic according to current methods of tissue oxygen determination i e the brain Using the brain of the rat we *have attempted to determine the radiosensitivity of the cerebral tissue and the* dose modifying effect of nitrogen breathing before and during irradiation of the brain

Materials and Methods Two-hundred and thirty Wistar albino rats of both sexes aged between 11 and 19 weeks were subjected to electron beam irra diation from an 8 MeV linear accelerator Anaesthesia was induced with an intraperitoneal injection of 40 mg/kilo bodyweight of methohexitone sodium

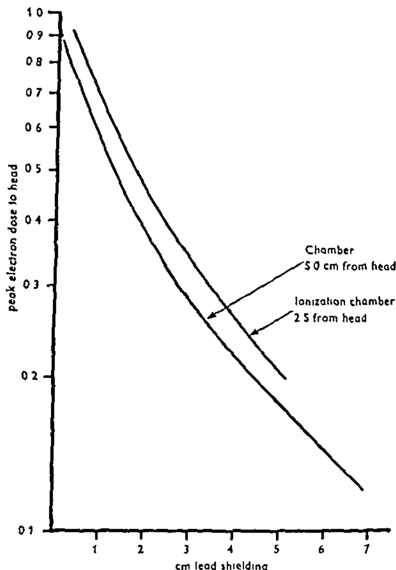


Fig 3 Effect of lead shielding on whole body dose to rat when treating a local field on the head

chosen for its rapidity of onset and clearance, so that respiratory depression due to the barbiturate was kept to a minimum Anaesthesia was maintained on an air plus ether mixture delivered from a purpose built anaesthetic machine The machine allowed close control of the volumes of gases given to the animals by using rotameter tubes calibrated from 100 to 1 000 ml, and rapid changes could be made from one gas to another by the incorporation of solenoid controlled valves in the gas lines The final gas mixture was administered to the rat via a close fitting face mask

Tissue oxygen' studies were carried out using polarographic needle elec

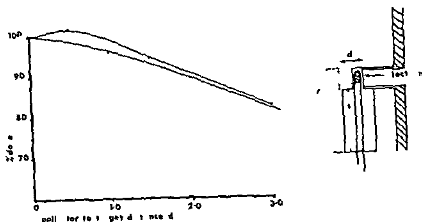


Fig 4 Techn que and dose measurements to assess final dose on increase of focal skin distance

trodes after the type described by CATER et coll (1957) We used 200 μ Diamel coated platinum wire mounted in the shaft of a No 20 hypodermic needle with ARAL AT100/HY100 to give extra insulation The face of the wire was ground off parallel to the bevel of the needle and polished These recording electrodes were inserted singly into the fore brains of rats through fine burr holes made in the parietal area of the skull, a silver/silver chloride reference electrode was placed subcutaneously in one flank A polarising voltage of 0 6 volt was used The current developed by the system was recorded on a re cording micrograph (Kipp & Zonen type BD2 or BD3) set at 0 1 microamp sensitivity

The source of radiation was the electron beam of the 8 MeV linear accele rator at the Radiotherapy Research Unit of the Medical Research Council, Hammersmith Hospital This unit was chosen for two reasons The first was that the machine could maintain a sustained high dose rate per minute with minimum run up time before peak output Secondly the type of radiation was in current use for therapy and research work so that the machine was fully calibrated The dose rate utilised was 35 kilorad per minute, using a short tunnel between the scattering foil window and the head of the animal under going irradiation giving an effective focal distance of 91 cm The exit port was an acrylic tube applicator of 1 5 cm internal diameter This diameter was the optimum size available in relation to the rat s skull since a smaller internal dimension would have caused too great a fall off' in dose on moving laterally off the central beam axis (Figs 1 and 2) These figures al o show the rapid fall off at depth of the beam which minimised radiation reactions on the

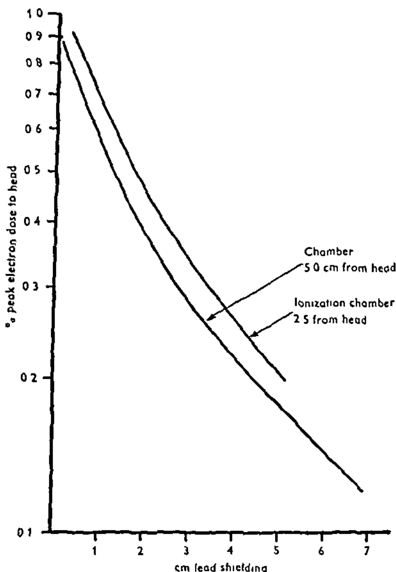


Fig 3 Effect of lead shielding on whole body dose to rat when treating a local field on the head

chosen for its rapidity of onset and clearance, so that respiratory depression due to the barbiturate was kept to a minimum Anaesthesia was maintained on an air plus ether mixture delivered from a purpose built anaesthetic machine The machine allowed close control of the volumes of gases given to the animals by using rotameter tubes calibrated from 100 to 1 000 ml, and rapid changes could be made from one gas to another by the incorporation of solenoid controlled valves in the gas lines The final gas mixture was administered to the rat via a close fitting face mask

'Tissue oxygen' studies were carried out using polarographic needle elec

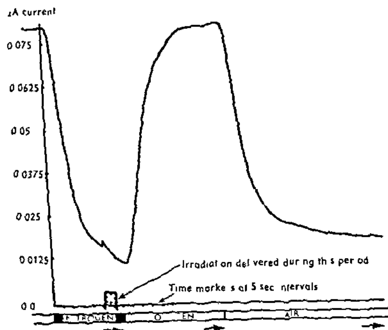


Fig 6 Rat brain irradiation whilst breathing 100 nitrogen

(Boulton Paul Ltd type F 16) was used to display respiratory movements on Pendeford multimeter C21 mark II (Boulton Paul Ltd)

Results

Preliminary investigations with the tissue oxygen electrode in the brains of anaesthetized rats given various concentrations of oxygen and nitrogen to breathe had shown that a rat could be maintained on 100 % nitrogen for between 50 and 60 seconds with a good chance of survival without any obvious respiratory or neurological sequelae

The decline in current recorded from the brain, when animals were switched from 100 % oxygen to 100 % nitrogen as the inspired gas are shown in Fig 5, giving the mean values for 31 rats including plus or minus one standard error The values are expressed as a percentage of the maximum deflection recorded with the rat breathing 100 % oxygen

This mode of expression was chosen because the calibration of this form of electrode in terms of absolute partial pressures of oxygen is open to question In tissue the current recorded at the tip of the electrode is proportional to the

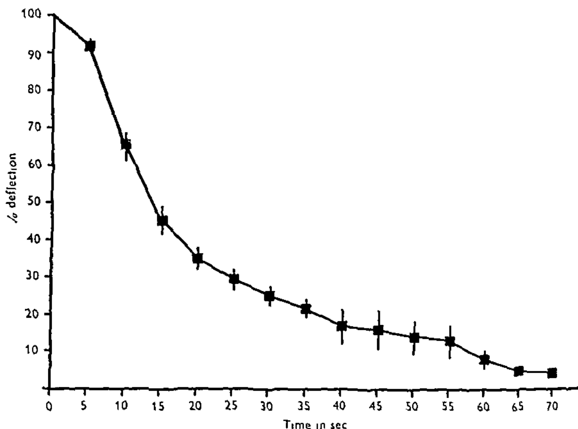


Fig 5 Decline in current recorded from brain during nitrogen breathing

structures in the pharyngeal region It was anticipated that the body of the rat would receive a quantity of roentgen radiation derived from scatter during exposure of the brain to the electron beam To assess this factor, dose measurements were made with an acrylic rat phantom containing a thimble ionisation chamber and bolus to occupy the residual air spaces The dose on the midline of the 'rat' was recorded with the chamber at the head, 2 5 cm into the trunk from the head, and at 5 0 cm from the head The results of this procedure, and the reduction in body dose effected by increasing the thickness of lead shielding between the wall of the applicator and the body of the phantom are shown in Fig 3 In animal experiments involving the use of a tissue oxygen electrode in the brain at the time of irradiation, it was necessary to increase the focal skin distance to allow the electrode to clear the end of the applicator

Dose measurements were made as in Fig 4, the final dose being increased to compensate for the extra distance A closed circuit television unit (Pye Ltd) was used for viewing the animal during irradiation and a transducer

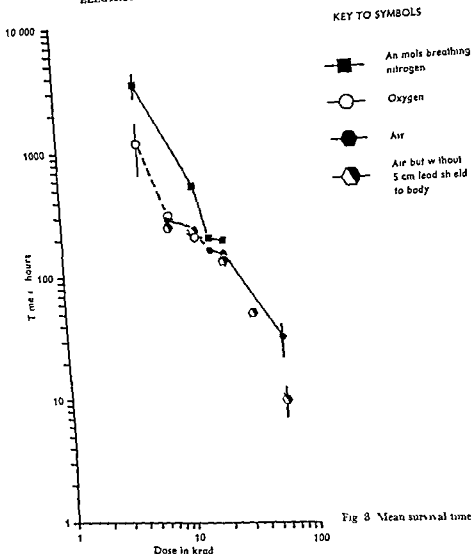


Fig 8 Mean survival times

and in Fig 7 the course whilst the rat breathed 100 % oxygen during the procedure With the dose rate available we aimed to commence radiation after 35 seconds of 100 % nitrogen breathing for animals irradiated with doses from 4 700 rad to 21 380 rad These high doses were used to try and demonstrate the existence of the nitrogen dose modification on a rapid all or none basis Rats were also given 35 500 rad and 58 700 rad but only whilst breathing air

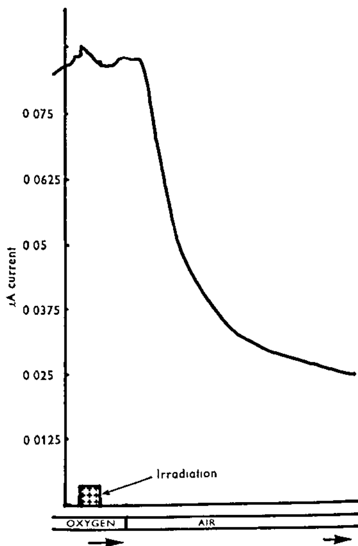


Fig 7 Rat brain irradiation whilst breathing 100 % oxygen

remainder of the sum oxygen arriving at the tissue in the region of the electrode minus oxygen consumed by the tissue, and hence such types of electrode should be known as 'surplus oxygen' electrodes Also no calibrating 'cell' has yet been devised that both supplies and consumes oxygen, so it did not seem correct to carry out direct calibration experiments in vitro and use the results for in vivo readings We preferred to internally calibrate the electrode in the animal since our electrodes were large and gave only relative values of the 'surplus oxygen' in a large area of cerebral tissue

Actual recordings made whilst the rat s brain was being irradiated are given in Figs 6 and 7, in Fig 6 the course when the animal breathed nitrogen,

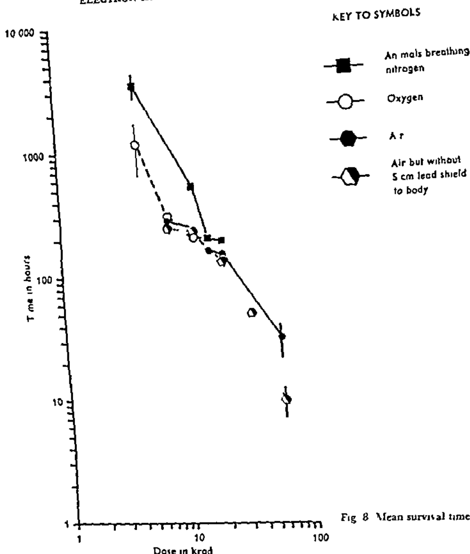


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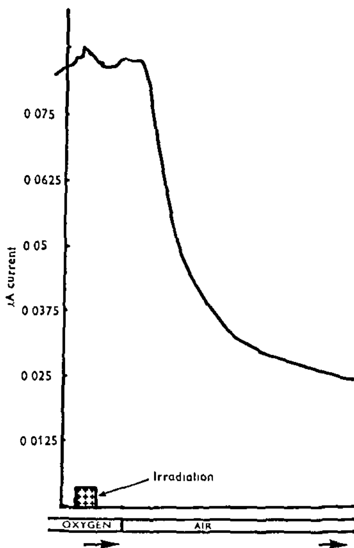


Fig 7 Rat brain irradiation whilst breathing 100 oxygen

remainder of the sum oxygen arriving at the tissue in the region of the electrode minus oxygen consumed by the tissue, and hence such types of electrode should be known as 'surplus oxygen' electrodes Also no calibrating 'cell' has yet been devised that both supplies and consumes oxygen, so it did not seem correct to carry out direct calibration experiments in vitro and use the results for in vivo readings We preferred to internally calibrate the electrode in the animal since our electrodes were large and gave only relative values of the 'surplus oxygen' in a large area of cerebral tissue

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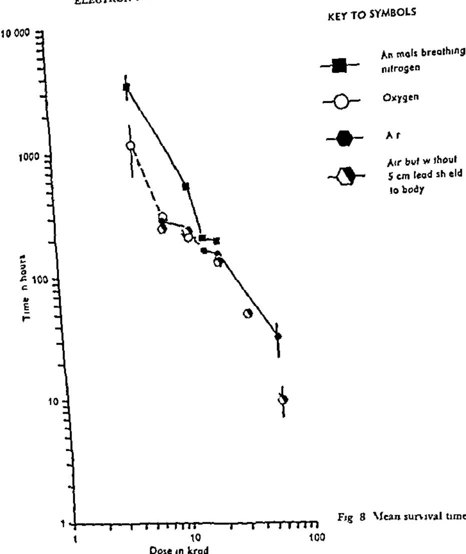


Fig 8 Mean survival times

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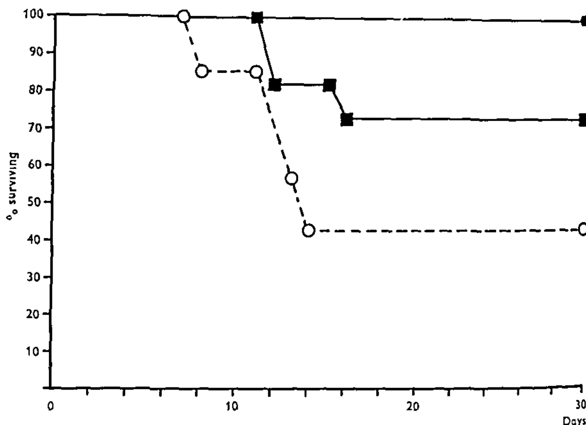


Fig 9 30 day survival pattern dose to brain 4 700 rad For key to symbols see fig 8

The general shape of the mean survival time curve in Fig 8 conforms to the pattern found by RAJEWSKY (1954) though the plateau where the survival time remained constant in spite of increased dosage of irradiation extended in our series from 8 500 rad to 20 000 rad, whereas Rajewsky's plateau ranged from only 1 200 rad to 15 000 rad The marked shortening of the survival time after a dose of 58 700 rad with the rat breathing air, demonstrates that one has passed down the shoulder of the curve We noted that at 35 500 rad and at 58 700 rad the presence of the extra 2 inches of lead shielding to the body of the irradiated animal exerted an effect on the survival times (Figs 3 and 8) In the dose range 16 600 rad to 21 380 rad we could not demonstrate any significant modification of the survival pattern by giving the animals nitrogen instead of air or oxygen to breathe, though the nitrogen breathers did have slightly longer mean survival times

	Oxygen	Air	Nitrogen	
21 380 rad	136	147	186	hours
16 600 rad	19?	158	197	hours

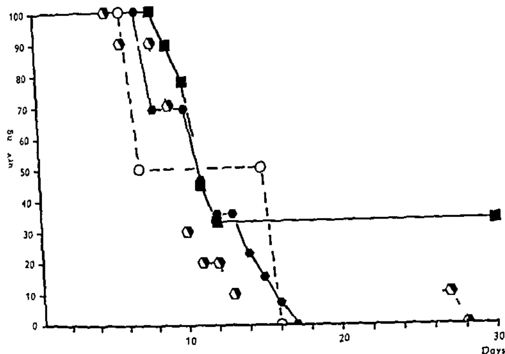


Fig 10 30 day survival pattern dose to brain 7 800 rad For key to symbols see fig 8

Between 12 800 rad and 4 700 rad the oxygen and nitrogen survival lines diverge but do not run parallel to each other There is an apparent time of survival equivalence at 6 000 rad under oxygen to 11 500 rad under nitrogen giving a dose modification factor of 1 9

The 30 day survival patterns as shown in Figs 9 to 12 disclose that 43 % of the animals survived 30 days after receiving a dose of 4 700 rad whilst breathing oxygen at the time of irradiation whereas 41 % of the animals who breathed nitrogen at the time of irradiation survived 30 days after a dose of 12 800 rad a dose modification factor in this case of 2 7

Discussion

There is no doubt that a sufficient lowering of the oxygen content of cells results in a modification of the effects of irradiation allowing the cell to survive incident doses of irradiation that would kill a fully oxygenated cell This effect

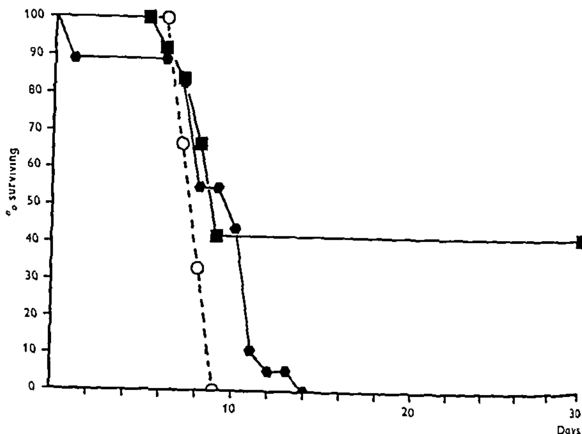


Fig 11 30 day survival pattern dose to brain 12 300 rad For key to symbols see fig 8

was first demonstrated by HOLTHUSEN (1921) who showed that Ascaris eggs in the anaerobic state required three times as much roentgen radiation to prevent their hatching as eggs irradiated under aerobic conditions Similar results have been obtained with isolated cell cultures, single organs such as thymus or tail, and for whole body irradiation VAN DEN BRENK (1963) in his work on tourniquet anoxia accepts a figure of 2 7 From our results with rats' brains we have been unable to demonstrate a consistent degree of modification of the effect of irradiation by anoxia The 25 day survival equivalence of 6 000 rad in oxygen to 11 500 rad in nitrogen represents only a modification of 1 9, and the alteration in 30 day survival only held for 4 700 rad in oxygen to 12 800 rad in nitrogen This improvement in survival would hardly be considered worthwile from a tumour therapy standpoint, even though our doses are rather beyond the accepted therapeutic range

As to the inconsistency in our results a simple explanation could be that we didn't render the brains of our rats sufficiently anoxic before commencing irradiation As 83 % of the animals that were irradiated whilst breathing

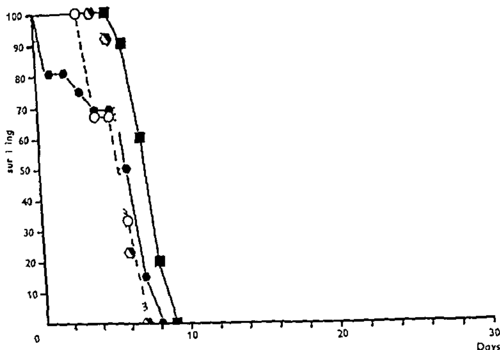


Fig 12 30-day survival pattern dose to brain 21 380 rad For key to symbols see fig 8

nitrogen stopped breathing before the end of irradiation, and required revival by artificial respiration, we think that our rats reached critically low levels of oxygen tension for some groups incurred a 10 % mortality because the animals didn t restart respiration In our hands 60 seconds of breathing 100 % nitrogen was the tolerable limit that would give the rat a good chance of survival for to try and increase this time was to risk killing the brain tissue by hypoxia alone which would have confused the situation Readings from our platinum electrodes show that the brain quickly becomes anoxic when the animal is given nitrogen to breathe DAVIES & BRONK (1957) using more refined methods claim that cerebral tissue is always on the brink of oxygen lack CROSS & SILVER (1962 have shown that there is some variation in the current recordable and hence in tissue oxygen concentration even in closely related parts of the brain Our experience confirms this We had hoped to use the polarographic system as a monitor to indicate when irradiation could commence but in irradiated rats the prolongation of anaesthesia necessary to

effect suitable placement of the electrodes caused further hazard to the animals Precise information of the actual levels of oxygen concentration in cerebral cells is not available, and one must avoid the circular argument that brain tissue can only be truly anoxic when dose modification can be demonstrated The question awaits the introduction of a method of measuring intracellular oxygen tensions that do not interfere with the cell's metabolism, and can be accurately calibrated in terms of partial pressures of oxygen with values directly referable to cells in tissue

The mechanism whereby irradiation causes death is another factor that must be considered Death of the brain following irradiation can be grossly divided into that caused by destruction of brain cells or permanent impairment of their metabolism, and that caused by alterations to the blood supply These factors cannot readily be separated though one series of changes may appear to dominate Death from the high doses of irradiation with the animal surviving only a few hours or days is thought to be primarily due to death of brain cells although this is uncertain In the symposium on the 'Response of the nervous system to ionizing radiation' (1962), no one seemed to be able to give a definite opinion supported by experimental evidence The brains of our rats who died after high doses of irradiation showed marked oedema and small areas of haemorrhage When death occurred months after a lower dose of irradiation the blood vessels showed more extensive changes with thrombus formation The brain substance was markedly necrotic in both grades of irradiation Therefore anoxia, to be truly effective, must protect not only the cells comprising the brain tissue, but also the blood vessels from the effects of irradiation The brain is at a disadvantage compared to other tissues following trauma of any form, since it cannot replace dead neurons with new cells of the same function It may be that nitrogen does protect a percentage of cells in any tissue, which, if these can grow and divide and replace the dead cells, can restore full function to the tissue, but that in the brain the percentage of cells surviving is not high enough to ensure continued function of the brain as an integrated unit

Since this paper was prepared, the dose range has been extended to include groups irradiated in air, oxygen, or nitrogen at 1 010 rad and 2 030 rad All groups show a 100 per cent 30 day survival

Acknowledgements

We wish to thank Dr L A Wright for his guidance and Mr P D Laming for his technical assistance We also thank Mrs A Silvester (Hammersmith Hospital) for her preparation of the physical dose measurements and Mr G Harding for his help with the linear accelerator

SUMMARY

The brains of rats have been irradiated with 8 MeV electrons whilst the animals breathed 100% nitrogen before and during irradiation No consistent degree of dose modification effect by nitrogen in the dose range 4 700 rad to 21 380 rad was shown The level of hypoxia necessary to achieve dose modification is thought to be too close to that which causes brain cell death by itself The inability of the brain to regenerate functional neurons is probably another factor

ZUSAMMENFASSUNG

Die Gehirne von Ratten wurden mit 8 MeV Elektronen bestrahlt wobei die Tiere vor und während der Bestrahlung 100 % Stickstoff einatmeten Bei Stickstoffatmung ergab sich im Bereich von 4 700 bis 21 380 rad kein bestehender Unterschied Es wird vermutet dass der Grad von Hypoxie der notwendig wäre um Dosismodifikationen wirksam zu machen zu nahe dem Zustand ist der den Zelltod selbst zur Folge hat Die Unfähigkeit des Gehirnes funktionelle Neurone zu regenerieren ist wahrscheinlich ein weiterer Faktor

RESUMÉ

Le cerveau de rats a été irradié par des électrons de 8 MeV pendant que ces animaux respiraient de l azote pur avant et pendant l irradiation On n a pas observé de modification constante de la dose sous l effet de l azote entre 4 700 et 21 380 rad Les auteurs pensent que le degré d hypoxie nécessaire pour entrainer des changements de dose est trop proche de celui qui par lui meme cause la mort des cellules cérébrales L incapacité du cerveau a régénérer des neurones fonctionnels est probablement un autre facteur

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FROM THE DEPARTMENTS OF RADIOTHERAPEUTICS (PROF. J. S. MITCHELL) AND PATHOLOGY (PROF. R. I. N. GREAVES), THE UNIVERSITY OF CAMBRIDGE, ENGLAND

COMBINED THERAPY WITH 220 KV ROENTGEN AND 5-HYDROXYTRYPTAMINE OR CYPROHEPTADINE IN RAT HEPATOMA

by

DONALD B. CATER and CONSTANCE A. GROVE

CATER, SILVER and WATKINSON (1964) found that 2 620 R of 220 kV roentgen rays and subsequent 10 cm microwave heating of the tumours to 47° C for 8 to 10 min. cured some rats with hepatoma 223 transplanted in the leg, whereas there were no long term survivors in rats treated by radiation alone or diathermy alone. In these experiments the heating of the tumours to 47° C for 8 to 10 min. would be expected to liberate 5-hydroxytryptamine (5-HT) and histamine from damaged tumour cells and this could lead to inflammatory thrombosis of tumour vessels with subsequent degeneration of the tumour. There was also evidence from the experiments of CATER, GRIGSON & WATKINSON (1962), CATER, SCHOENIGER & WATKINSON (1963) and CATER, PETRIE & WATKINSON (1965) that 5-HT caused marked slowing of blood flow in tumours which would be expected to favour thrombosis of tumour blood vessels. CRILE (1963) found tumours in vivo much more susceptible to the destructive

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Table

Effects of 5-HT or cyproheptadine alone or following radiation on hepatoma 223 in rats

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Treatment						
Radiation	0	0	0	2 620 R	2 620 R	2 620 R
Injection	Saline	5 HT	Cyproheptadine	Saline	5 HT	Cyproheptadine
Survival						
Range	11 to 55	11 to 41	12 to 38	15 to 112	8 to 115	19 to 110
Mean	27 65 ± *1 44 (31)*	26 1 ± *1 65 (32)*	26 3 ± *1 5 (25)*	41 5 ± 3 75 (31)	37 6 ± 3 86 (32)	48 3 ± 4 15 (25)
Primary tumour						
Mean size at death	45 6 ± [illegible]1 (31)	36 5 ± 52 (32)	*37 1* ± 55 (25)	12 ± *2 6 (31)*	3 [illegible] ± *0 8 (32)*	9 7 ± [illegible] *(25)*
Response to treatment						
(a) Temporary decrease in size	0/31	12/32	0/25	30/31	32/32	25/25
(b) Temporary disappearance during *treatment*	*0*	*0*	*0*	*10/31*	18/32	9/25
Metastases in						
Aortic nodes	18/23	21/32	13/22	27/31	9/30	22/25
Mean size at death	4 8 ± 1 5 (23)	*7 4* ± 1 5 (25)	*1 95* ± 0 7 (22)	*20 1* ± *2 9 (31)*	15 8 ± *3 (30)*	29 9 ± *5 25 (25)*
Inguinal nodes	10/31	11/32	9/25	12/31	7/30	8/25
Axillary nodes	2/31	2/32	0/25	2/31	3/30	2/25
Lungs	*10/11*	12/16	7/9	14/19	12/22	*18/22*
Thymus	*0/11*	*0/16*	1/9	1/19	1/22	4/22

Results

Data from the 5 experiments have been pooled *and are* summarized in the Table The mean survival times of the three unirradiated control groups (1 2 and 3) were almost identical Twelve out of 32 of the primary tumours of group 2 (treated with 5 HT) showed a temporary *reduction in* size during the period of 5 HT treatment but the mean size of *the primary* tumour at death was the same as the cyproheptadine treated controls *(group 3)* and was not significantly smaller than the saline treated controls *(group 1)* The incidence of spread to aortic inguinal and axillary lymph nodes *was* comparable in the three groups

The three irradiated groups (4 5 and 6) *showed no* significant differences in their mean survival times There *were no long* term survivors If the 6 early deaths due to 5 HT toxicity are removed *from* group 5 the mean survival

effects of heat than tumour cells in vitro and suggested that this was due to a heat induced inflammatory reaction impairing tumour blood flow He found that injecting 2 5 mg 5 HT into mouse tumours immediately before heating greatly increased the susceptibility of the tumour to heat On the other hand, SCOTT, SCHELINE & STONE (1958) and COMVALIUS (1960) suggested that 5 HT might produce conditions favourable for the growth of tumour cells Experiments were therefore set up to see if radiotherapy followed by a series of injections of 5 HT would have a similar effect to radiotherapy followed by microwave diathermy heating It was also decided to study the effect of radiotherapy followed by injections of the anti 5 HT, antihistamine drug cyproheptadine

Material and Methods Male rats of the August strain were injected in the left leg with 0 2 ml of transplantable hepatoma 223 (maintained as an ascites tumour) After 5 days they were randomly allocated into 6 groups Control groups 1, 2 and 3 were given sham treatment and subsequently injected with saline, 5 HT, or cyproheptadine respectively Groups 4, 5 and 6 were irradiated and subsequently injected with saline, 5 HT or cyproheptadine respectively Six or 8 days after tumour innoculation the rats to be irradiated were wrapped in lead with the left thigh protruding through a hole in the lead, and irradiated with a 220 kV 'Maximar using a 5 cm circle applicator to the dorsal aspect of the thigh and leg A dose of 2 620 R was given (dose rate 164 R/min with back scatter), FSD 41 5 cm and 1 mm Al as filter

Five experiments were made In experiment 1, groups 1, 2, 4 and 5 were used, the irradiation was 6 days after tumour innoculation and injections of saline or 5 HT (serotonin 5 mg base/kg rat) were given intraperitoneally, daily on day 7, 8, 9, 10 and 11 About half of the rats injected with 5 HT died about the 10th to 13th day so that in experiment 2 (irradiated on the 8th day), the 5 HT was given subcutaneously, daily, into different sites on day 9, 10, 11 and 12 Again a number of rats died about the 13th to 15th day so that in experiments 3, 4 and 5, the injections were given on alternate days, 6 injections, the first being given 1 hour after irradiation Thus in experiment 3 (irradiated on day 8), saline 5 HT, 5 mg base/kg, S C, or cyproheptadine 2 mg/kg S C was given on day 8, 10, 12, 14, 16 and 18 and in experiments 4 and 5 (irradiated on day 6) the injections were given on day 6, 8, 10, 12, 14 and 16 By this method the accumulated toxicity of the 5 HT was avoided Groups 1 to 6 were used in experiments 2 to 5 The length, breadth and thickness of all tumours were measured with calipers at frequent intervals At autopsy, careful examination was made for metastases and material was taken for histologic examination of the primary tumour, and in doubtful cases histologic examination of the lungs was made for metastases

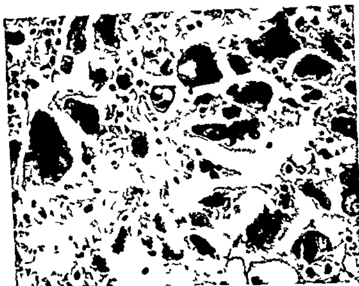


Fig 2 Giant cells and cells with bizarre nuclei which was a common finding after irradiation of the tumour and treatment of the rat with 5 HT H and E × 400

3 The mean size at death of the primary tumours in the irradiated 5 HT-treated group was significantly smaller than either of the other irradiated groups (see Table) group 5 against group 4 gave students $t = 3.16$, $n = 61$ $p < 1\%$, $> 0.1\%$ and for group 5 against 6, $t = 2.86$, $n = 55$ $p < 1\%$

There was evidence of some reduction in metastases in the irradiated 5 HT treated group The number of rats with involvement of the aortic nodes (see Table) was highly significantly less in this group than in the other irradiated groups This was still true if the 6 early toxic deaths were eliminated from the calculations The mean size of the aortic nodes at death was 15.8 ± 3 (30) compared with 29.9 ± 5.25 (25) in the irradiated cyproheptadine treated group $t = 2.34$ $n = 53$ $p = 2\%$ The incidence of inguinal node involvement was slightly less and the number of rats with secondary deposits in the lungs was also less (see Table) An interesting finding was that 4/22 of the rats of group 6 had metastases in the thymus and some of the rats in this group showed diffuse invasion of the tumour into the mesentery of the gut

Histologic examination showed that about half of the primary tumours of the irradiated 5 HT treated group (5) had giant cells compared with a much smaller incidence in groups 4 and 6 These giant cells embedded in

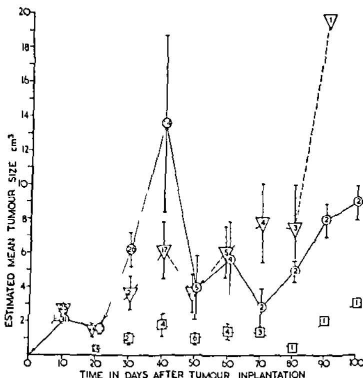


Fig 1 Means of estimated tumour volumes in the three irradiated groups plotted at 10 day intervals after tumour implantation Irradiated and injected with saline (group 4) — — ▽ — Irradiated and injected with 5 HT (group 5) □ Irradiated and injected with cyproheptadine (group 6) ——○— The number of rats surviving at each interval of time and the standard errors of the means are indicated

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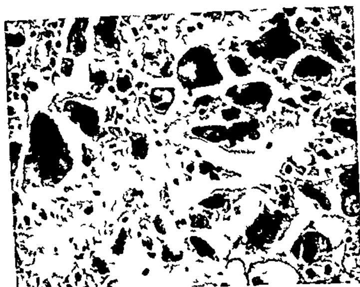


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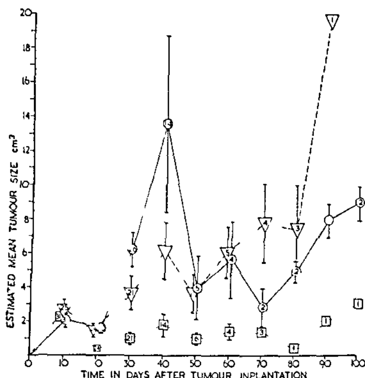


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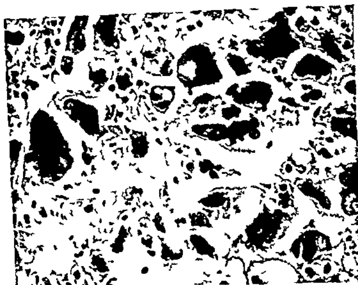


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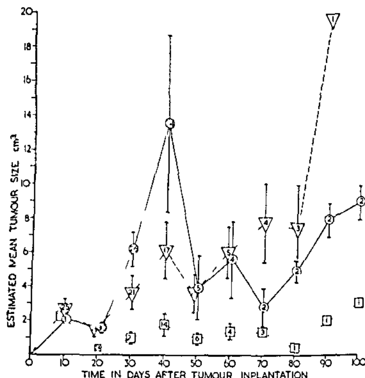


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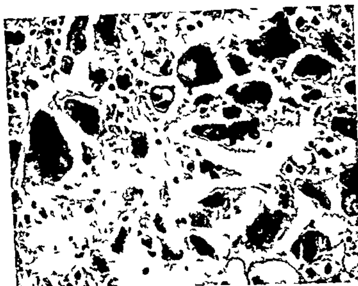


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Discussion

Hepatoma 223 injected into the legs of August strain rats could not be cured by radiotherapy with 2 620 R, 220 kVp roentgen rays, and there were no long term survivors in the irradiated rats which were subsequently given a course of injections of 5 HT or cyproheptadine Therefore the therapeutic effect of microwave heating after radiotherapy (CATER, SILVER & WATKINSON 1964) was not imitated by 5 HT treatment under the experimental conditions used Rather different experimental conditions were used by CRILE (1963) *who found that 2 5 mg serotonin injected into the tumour in transplanted* tumours in mice greatly increased the effectiveness of heat treatment of the tumours Histamine or angiotonin also increased the therapeutic effect of heat It will be noted in the experiments on hepatoma 223 now described that, after radiotherapy, treatment of the rats with 5 HT reduced the growth rate of the tumours and gave a greater number of temporary remissions compared with radiotherapy alone Also CRILE (1963) found that 2 5 mg of serotonin daily for 3 weeks inhibited the growth rate of S 91 melanoma in mice This inhibitory effect of 5 HT on the growth rate of tumours could be due to at least three different effects of 5 HT

Firstly, 5-HT might inhibit the growth of tumours by the shock like state that often follows its injection Shock is known to reduce the growth rate of tumours in experimental animals Shock will cause an increased output of corticosteroids from the adrenal cortex and these will have an anti mitotic effect Also in shock the blood pressure is lowered and this will reduce the blood flow through tumour and reduce the oxygen tension in tumour (CATER, GRIGSON & WATKINSON 1962)

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of 5-HT because it was reversed or inhibited by an anti 5HT agent REDDY, ADAMS & BAIRD (1963) found that serotonin was teratogenic when given to pregnant rats and suggested the possibility that this might be due to the effects of 5 HT on blood vessels

Thirdly, 5 HT might have a direct effect on the growth or spread of tumour cells The experiments described here indicated a reduced rate of tumour growth in the irradiated and 5 HT treated rats and also less spread to the aortic lymph nodes Even if the early toxic deaths are removed from the 5-HT treated group there is still a highly significant reduction in the aortic node involvement and the size of the aortic nodes at death compared with the group treated after irradiation with cyproheptadine However, in the literature there is evidence both for an inhibitory action of 5 HT on tumour growth and for a stimulatory action Thus SCOTT, SCHELINE and STONE (1958) and SCOTT (1963) found that giving 5 HT (1 3 mg/rat/day) starting two days prior to implantation produced larger tumours than in the controls When starting one day prior to implantation of 5 HT (1 3 mg) and histamine (1 1 mg) also gave larger tumours than in the controls Degranulation of the mast cells by treatment with distilled water tumour polypeptide or reserpine, decreased the growth of transplanted tumours and the percentage of takes COMVALIUS HOWARD & STRAWITZ (1963) found that if Walker 256 tumour cells were allowed to age in saline at room temperature for 1 to 7 hours to reduce their viability the percentage of successful transplants was increased in rats treated with 5 HT (0 4 mg I M) immediately after transplantation and daily for 7 days MCDONALD SCHMID HAKALA & MALLORY (1959) found that a single dose of serotonin (40 mg/kg S C) increased mitosis and incorporation of tritiated thymidine in hepatic cells of young rats weighing less than 115 g PUKHALSAYA (1964) using 5 HT (10 mg/kg/day) for 10 days found increased mitosis in regenerating liver and in intestinal mucosa and a three fold increase of neutrophils in the blood

Several observers have described the increase of mast cells in precancerous skin treated with chemical carcinogens (COUPLAND & RILEY 1960 SIMPSON 1963 BENDITT HOLCENBERG & LAGUNOFF 1963) and in rat and mouse these mast cells show evidence of 5 HT However CHIECO BIANCHI FIORE DONATI PENNELLI & BERTACCINI (1963) describe a similar mast cell accumulation in the precancerous skin of hamsters painted with 9 10 dimethyl 1 2 benzanthracene but these mast cells contain no significant quantity of 5 HT In fact the presence of 5 HT in mast cells appears to be confined to the rat and the mouse RILEY (1963) and BENDITT HOLCENBERG & LAGUNOFF (1963) stress that in man and other mammals histamine serves the part played by 5 HT in the rat and mouse Moreover, the precise role of the mast cells in

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ZUSAMMENFASSUNG

Kombinierte Therapie von 2 670 R bei 220 kV und darauffolgende Injektion von 5 HT war erfolglos in der Behandlung von Ratten des August Stammes mit Hepatom 223 das in das Bein transplantiert war Es gab jedoch bei diesen vorbehandelten Ratten mehr temporare Remissionen weniger und kleine Metastasen und die durchschnittliche Tumorgrosse war geringer als bei jenen Ratten die mit Kochsalzlosung oder mit dem anti 5-HT Mittel Cyproheptadine behandelt worden waren

RÉSUMÉ

L association de 2 620 R de roentgenthérapie a 220 kV et d un traitement par injection de 5-HT n a pas guéri des rats de souche August porteurs d hépatome 223 greffé sur la patte Cependant les rémissions temporaires ont été plus nombreuses le volume moyen de la tumeur etait plus petit et les metastases étaient moins nombreuses et plus petites chez les rats traités par 5-HT apres radiothérapie que chez ceux qui avaient été traités par une solution salée ou par un agent anti 5-HT la cyproheptadine

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carcinogenesis is uncertain, they could be part of the defense reaction promoting a fibrous tissue barrier against the tumour or they could be instrumental in stimulating tumour growth Information contained in PUKHALSKY's (1964) paper may provide the answers to some of the contradictions outlined above He finds that 5 HT is only inhibitory against transplanted tumours if it is given in the form of 5 HT hydrochloride and not if given as the creatinine sulphate, and only if injected subcutaneously and not intraperitoneally Also, finding that 5 HT stimulates haematopoiesis, and mitotic activity in regenerating liver and intestinal mucosa, but inhibits mitosis in the growing tails of tadpoles, he suggests that 5 HT inhibits mitosis but that its metabolic product, 5 indol acetic acid, stimulates mitosis in animals as in plants He suggests the use of monoamine oxidase inhibitors to increase the antimitotic effect of 5 HT

Our own findings suggest that 5 HT after radiotherapy was inhibitory to tumour growth and spread, especially when compared with the rats treated with the anti 5 HT drug cyproheptadine We think that 5 HT could cause circulatory stasis in a tumour and by inducing thrombosis produce a mild version of the acute degeneration of tumour caused by SHEAR's polysaccharide (SHEAR 1941, SHEAR & PERRAULT 1944) Our finding of the more frequent presence of multinucleated cells in the 5 HT-treated tumours would be consistent with an antimitotic effect for 5 HT (e g the effect of radiation) It is important to note that the concentration of oxygen is a rate limiting factor in monoamine oxidase activity so that of 5 HT might have a more prolonged action on the zones of low oxygen tension in a tumour than on normal tissues CRILE's method of injecting 5 HT direct into a tumour might be the most effective method of treatment PUKHALSKY's suggestion of using monoamine oxidase inhibitors merits further investigation

Acknowledgements

Financial help from the British Empire Cancer Campaign for Research is gratefully acknowledged (D B C received full time support and C A G part time) Our warm thanks are due to Professor J S Mitchell for advice and encouragement and to Mr Eric King and Mrs F Allen for technical assistance

SUMMARY

Combined therapy with 2 620 R of 220 kV roentgen rays and subsequent injection treatment with 5 HT failed to cure August strain rats with hepatoma 223 transplanted in the leg However there were more temporary remissions the mean tumour size was smaller and there were fewer and small metastases in rats treated with 5 HT after radiotherapy than those treated with saline or the anti 5 HT drug cyproheptadine

FROM THE DEPARTMENT OF RADIOTHERAPEUTICS (DIRECTOR PROF J S MITCHELL),
UNIVERSITY OF CAMBRIDGE, ENGLAND

WHOLE BODY COUNTER IN ROUTINE TESTS OF HYPERTHYROIDISM USING IODINE 131

by

R A POPE

It was clear from the papers presented at the Symposium on Whole Body Counting (I A E A 1962) that most of the associated instrumental and development problems had been overcome, and that whole body counting techniques were already being applied to clinical problems Much credit must be given to the early workers who used high pressure ionization chambers with a sensitivity approaching the natural γ activity of the body and who were largely concerned with the body retention of thorium and radium products (SIEVERT 1950, BURCH 1952 BURCH & SPIERS 1953 RUNDO 1955) Great stimulus for this work arose from the radiologic protection problems associated with the ingestion or inhalation of fission fall out products and contamination from nuclear establishments The estimate of body burdens and the time constants of retention became of world wide importance Technologic progress with scintillators and photomultipliers occurred at the same time (MARSHALL & COLTMAN 1947 BELL 1948 HOFSTADTER 1948) The development of large volumes of liquid phosphors for neutrino studies (COWAN et coll 1953) led to highly sensitive whole body counters using nearly 4π geometry (ANDERSON 1957) Thallium activated sodium iodide crystals were used by MARINELLI

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particularly susceptible to damage (HODGES et coll 1955 HALL & MYANT 1956 POTTER et coll 1959 GROSVENOR 1960, BROWN GRANT 1961)

It is attempted to show in the present investigation that a large reduction in dose is possible for thyroid studies in adults with the aid of a whole body counter Two techniques are described The first is performed with a scanning technique to determine the total body retention of ^{131}I The second is performed with a fixed crystal technique similar to a conventional thyroid uptake measurement except that two large uncollimated crystals are used in a low background steel room

Scanning technique

The urinary excretion of radioiodine has been used as a clinical test of thyroid function with considerable success (FRASER et coll 1953) The radioiodine excreted in the sweat is negligible (HARDEN & ALEXANDER 1963), and the loss in the faeces is very small (MYANT 1956) Therefore a retention study of radioiodine with a whole body counter will be the converse of a study with urinary collections The main problem in estimating the total body burden of ^{131}I with a whole body counter is the variation of the geometry of different subjects and the change in distribution of the isotope in the same subject with time Ideally any distribution of ^{131}I should give the same sensitivity in all subjects but unfortunately this is far from the case Allowance has to be made for the shielding effect of the body and the counting geometry at best can only approximate to 4π geometry CEDERQUIST & LIDEN (1961) showed that the ^{131}I retention can be more accurately measured by scanning than by using a sitting chair geometry

The object of this investigation was to determine whether total body measurements in adults would give as reliable a guide to the thyroid peak uptake as that measured by a conventional thyroid uptake technique If this was found to be true it was also important to see how the discriminating power of the peak uptake compared with the total information of peak uptake PBI 131 and in some cases the uptake of ^{131}I triiodothyronine (T_3) by red cells

Apparatus A scanning type whole body counter NE8102 was used (made by Nuclear Enterprises (G B) Ltd Edinburgh) and installed in their six inch thick steel room type SR 2 of length 245 cm width 168 cm and height 183 cm Two 6 × 4 inch crystals were used one above and one below a couch The maximum possible length of scan was 168 cm and this was used for all the subjects in this investigation Matching of the gain of the two heads and the overall gain of the system was maintained with the aid of a multichannel analyser and a cobalt 60 source

(1956), and RUNDO (1958), and plastic scintillators by BIRD & BURCH (1958) A thorough investigation of the means of reducing NaI (Tl) background counts with a steel room was done by MILLER et coll (1956) The use of chalk as a cheaper shielding material was described by TROTT et coll (1963) A survey of whole body counters that were in operation during 1962 (MEHL & RUNDO 1963, I A E A 1964) indicates that the largest use was for investigation of occupational contamination (DOLPHIN, MEGAW & RUNDO 1962)

Uses of iodine 131 Whole body counters that are capable of measuring the natural potassium 40 content of subjects offer the advantage in clinical studies of using radioisotope tracer techniques with very small administered doses of radiation, and also of avoiding the difficulties of complete collection of excreta over long periods

Perhaps the most widespread and frequent use of radioisotopes in non malignant conditions is the investigation of hyperthyroidism with ^{131}I, and it is natural that the possible application of whole body counters to this work should be assessed with the aim of reducing the radiological exposure Earlier reports (LUSHBAUGH 1961, LUSHBAUGH & HALE 1962, LUSHBAUGH 1963) showed that the thyroid in small animals and man could be studied by total body activity measurements The main disadvantage of using very small doses of ^{131}I is that the plasma protein bound radioiodine (PBI 131) cannot be measured and thyroid mapping cannot be performed However, the PBI 131 is sometimes misleading and the plasma butanol extractable iodine (BEI 127) could be used with advantage in its place, while thyroid mapping is of value only in a small number of special cases A common method of reducing the radiological dose to the thyroid is to use ^{132}I WAYNE, KOUTRAS & ALEXANDER (1964) suggested that the 2 1/2 hour thyroid uptake is less influenced by renal clearance than the 24 hour uptake, but it is more generally accepted that there is a wide equivocal range for early uptake measurements (HOBBS et coll 1963) Also there is always some ^{131}I impurity with the ^{132}I which increases the radio logical dose

In a 25 g thyroid, with peak uptake of 30 %, the average dose in euthyroid subjects is 1 6 rad per microcurie of administered ^{131}I, and 46 millirad per microcurie of administered iodine 132 (using the effective absorbed energy per disintegration as given by the I C R P 1959 Book of Recommendations and assuming an effective diameter of 3 cm) It is desirable to reduce these doses as much as possible in most groups of patients, particularly in women of child bearing age, all young people children, pregnant mothers and babies The metabolism of iodine in the mammary glands, the ovaries and the placenta is adapted to conserve the iodine of the foetus or the newborn which makes it

Table 1

Simple linear regression equations for thyroid peak uptake and total body retention of ^{131}I. The 48 hour retention gives the best correlation with thyroid peak uptake

Time after ingestion of ^{131}I	Percent peak uptake (Y) as dependent variable		Per cent total body retention (X) as dependent variable		r	P
	Linear regression equation	S_Y	Linear regression equation	S_X		
24 hours	$Y = 1.15X - 14.0$	9.6	$X = 19.2 + 0.72Y$	7.6	0.91	< 10
48 hours	$Y = 1.07X - 5.0$	8.5	$X = 10.5 + 0.81Y$	7.4	0.93	< 10
96 hours	$Y = $ [illegible]$6 + 0.95X$	11.5	$X = 10.9 + 0.76Y$	10.2	0.85	< 10

S_Y and S_X = standard error of estimate. P = probability using student's t test. r = coefficient of correlation.

A single scan was used in the whole body counter with a 2 1/2 min count. However, the 20 μCi ^{131}I involved a very high count rate in the whole body counter, and a correction had to be applied for the dead time of the counter. A single channel analyser was used with a relatively wide channel width from 270 to 450 keV. The overall dead time of the counting system was found to be 5 microsecond per count. A number of subjects had profile counts done on the whole body counter to estimate the true dead time correction, and it was found that this could be estimated to within 1 % from the integral counts.

The sensitivity of a point source of ^{131}I in the sagittal plane of a water filled polythene phantom having dimensions recommended by BUSH (1949) is shown in Fig. 1. The 100 % isocount curve is taken as the sensitivity that would be obtained if the point source was evenly distributed throughout the phantom. The values actually measured are shown by crosses and the isocount curves have been interpolated from them. The sensitivity of the thyroid is close to the sensitivity from an evenly distibuted source throughout the body. Hence the total body counts, even with much of the ^{131}I as extrathyroidal iodine, may be taken as a measure of retention provided the extrathyroidal radioiodine is homogeneously distributed. However, the sensitivity of ^{131}I in the stomach was less than in the thyroid.

The ratio of the thyroid to stomach sensitivity was estimated in thirty euthyroid patients who attended for the 96 hour count. It was assumed that at this time 5 % of the total body ^{131}I was extrathyroidal (BERSON & YALOW 1954). No significant difference was found between the mean thyroid to stomach sensitivity ratio in men and women, and a value of 1.23 was used for

Total time of count per scan = 2 5 minutes

0 25 min pause time at each end + 2 0 min scanning + 0 25 min pause time at each end

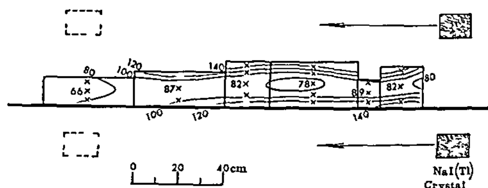


Fig 1 Relative positions of a human phantom and crystals for scanning to determine the total body iodine 131 Isocount curves in the sagittal plane of the body are also shown 100 % is taken as the sensitivity of the same source distributed evenly throughout the volume of the phantom The isocount curves were interpolated from measurements made in the positions marked with a cross

The subject lay supine as shown in Fig 1, with the top of the head 15 cm inside the start of the scan, although this positioning was not critical In order to correct for the limited length of the scanning distance, a pause time of 0 25 min was used at both ends of the scan with a scanning time of 2 min at 84 cm/min, giving a total counting time of 2 1/2 min each scan This is similar to the technique used by WORTHLEY (1962)

Method One hundred and twelve patients attending for routine ^{131}I thyroid uptake measurements were given 20 μCi ^{131}I with distilled water by mouth (sodium iodide 131 in dilute sodium thiosulphate solution, carrier free, supplied by the Radiochemical Centre, Amersham, England) and were then counted in the total body counter within ten minutes of ingestion of the dose while the iodine was still largely confined to the stomach (SMALL et coll 1961) They were allowed a light breakfast (TURELL et coll 1958, found that a light breakfast did not affect the 3 hour thyroid uptake) but they were previously cautioned against taking any food with a high iodine content Total body counts were repeated at 24 hours and 48 hours, and 64 of the patients were also measured at 96 hours after ingestion Thyroid uptake measurements were made at 4 hours, 24 hours 48 hours, and in the fewer cases at 96 hours They all had 48 hour PBI 131 measurements and some also had the red cell uptake of iodine 131 triiodothyronine estimated (HAMOLSKY et coll 1959, GOOLDEN et coll 1962)

Table 2

Arithmetic mean values for thyroid peak uptake, 24-hour thyroid uptake and 24, 48 and 96-hour total body retention of ^{131}I (R 24, R 48 and R 96), with the standard deviation (σ) assuming a normal distribution. The limits where there is an equal chance of a false negative as a false positive ($x \pm A\sigma$) are also shown. The value P is the percentage overlap at this limit. $A = \frac{x_2 - x_1}{\sigma_1 + \sigma}$ where x_1 and x_2 are the means of the two groups

	Hyperthyroid		Euthyroid		Hypothyroid		Hyperthyroid and euthyroid		Hypothyroid and euthyroid	
	Mean	σ	Mean	σ	Mean	σ	$x \pm A\sigma$	P	$x \pm A\sigma$	P
No. of subjects	4?		63		7					
Per cent peak uptake	72.2	10.9	33.4	11.6	14.3	5.9	53.4	4.2	20.8	13.8
Thyroid uptake at 24 hours ( )	68.9	9.7	31.5	9.5	13.6	7.0	50.0	2.6	21.2	14.0
R 24	72.7	11.1	41.6	9.2	36.0	11.2	55.7	6.3	39.1	39.2
R 48	70.0	11.0	36.9	9.9	21.4	11.9	52.6	5.7	29.9	23.9
R 96	66.9	11.6	35.8	11.4	15.0	12.0	51.2	8.9	25.7	18.7

Results

The correlations between the 24, 48 and 96 hour retentions (R 24, R 48, R 96) and the peak uptake were calculated with the simple linear regression equations and are shown in Table 1. Fig. 2 is a scatter diagram showing the 48 hour values. The grouping of hyperthyroid and euthyroid subjects was based when possible on the thyroid peak uptake, PBI 131 and T_3 measurements, and when these were conflicting the clinical picture was also taken into consideration. The diagnosis of hypothyroidism was based only on clinical grounds and only mild hypothyroid cases happened to be included.

The 24, 48 and 96 hour retentions all show significant correlation coefficients with the peak uptake, r = 0.91, 0.93 and 0.85, respectively, all with a probability $P < 10^{-4}$. The correlation for 48 hour retention is the best, probably because most of the inorganic iodine 131 and little of the organic iodine 131 had been lost from the body in hyperthyroid subjects. These results were also analysed by a method used by KUHNE et coll. (1955) and BRINKLEY et coll. (1957), where as a measure of reliability a normal distribution was assumed in the hyperthyroid, euthyroid and hypothyroid groups, and an index of percentage overlap calculated. The values of retention and uptake, where there is an equal likelihood of false negatives as of false positives, are shown in Table 2.

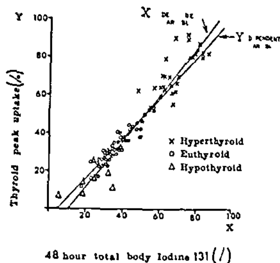


Fig. 2. Scatter diagram showing thyroid peak uptake and the 48 hour total body retention of ^{131}I. The simple linear regression lines whose equations are given in Table 1 are also shown.

both sexes in all the 112 cases. There was no correlation between the weight to height ratio, and the sensitivity of ^{131}I in the stomach, the thyroid, and the ratio of thyroid to stomach sensitivity. This implies that the average body diameter of an adult subject does not give any clear indication of the shielding effect of the body with this particular geometry. The variation of the sensitivity of ^{131}I in the stomach, the thyroid, and the ratio of thyroid to stomach sensitivity, all had a standard deviation of distribution of 13 %. This was taken as evidence that no greater error is involved when the subject is counted within 10 minutes of ingestion, and weighted by a factor of 1.23 for the 100 % retention, than if the administered dose is accurately measured before ingestion and the percentage retention calculated from the average thyroid sensitivity. Hence all total body retentions were calculated by the former method in this investigation.

As an additional check that the method of weighting did not involve additional errors, 15 patients had their 48 hour retention calculated by the method of weighting, and also by using the average thyroid sensitivity. The coefficient of correlation with peak uptake was + 0.94 and $P < 10^{-6}$ with each method. It appears that the shielding properties of the body for activities in the thyroid and the stomach are correlated in a way which is not simply represented by the weight to height ratio.

Mean sensitivities with standard error of the mean for a single scan and counting time of 2 1/2 min are:

Stomach: 25.9 ± 0.7 counts/nanocurie iodine 131/scan
Thyroid: 31.9 ± 0.9 counts/nanocurie iodine 131/scan
Background (room plus subject): 1.385 counts/scan

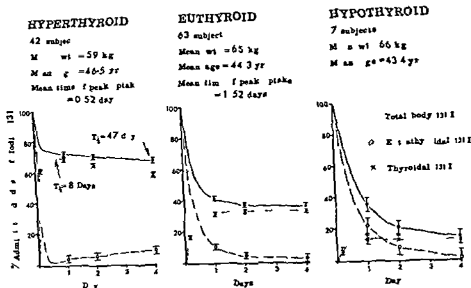


Fig 3 Arithmetical mean values for thyroidal extrathyroidal and total body iodine 131 Times of actual measurements are shown the extrathyroidal ¹³¹I was derived from the difference of the other two curves The standard errors of the mean are shown

To obtain the maximum information from the retention values the ratio $(R\,48)^2/R\,24$ was investigated as this represents the product of the 48 hour retention and an index for the gradient of the curve between 24 and 48 hours Unfortunately this ratio was found to be no improvement over the simple R 48 value and although it gave some promise as an improvement for discriminating hypothyroidism over the R 48 value it was no better than the R 96 value

It is felt that these results cast considerable doubt on the advisability of using any urine collection technique for investigating hypothyroidism The limits of normal thyroid peak uptake were given as 20 % and 55 % by BRINKLEY et coll (1957) which leads to 23 % and 56 % as the limits for 48 hour total body retention of iodine 131 in normals Using the upper limit of 56 % gives a probability of 2 7 % false positives and 10 2 % false negatives

The mean total body retention and thyroid content of ¹³¹I in the three groups of patients is shown in Fig 3 The extrathyroidal ¹³¹I is taken as the difference between the other two curves The lower renal clearance in hypothyroid subjects (MCCONAHEY et coll 1951, HLAD & PRICKER 1954 WAYNE, KOUTRAS & ALEXANDER 1964) accounts for the improvement in diagnosis of hypothyroidism with 96 hour retention compared with the 24 and 48 hour retentions The mean extrathyroidal ¹³¹I in euthyroid subjects at 24 hours is

Table 3

The 48 hour total body retention (R 48) of 11 patients who were tested with 0 1 μCi ^{131}I together with other investigations

Case	Date	Per cent thyroid peak uptake	Per cent R 48 with 0 1 μCi ^{131}I	Per cent R 48 with 20 μCi ^{131}I	Per cent PBI 131 per litre	Per cent T_3
1 Euthyroid large gain in weight	16 3 64	21	34	27	< 0 05	
2 Euthyroid tremor & nervousness	6 4 64	26	31	33	< 0 05	
3 Hypothyroid	6 4 64	7	10	6	< 0 05	
4 Euthyroid slight tachycardia	27 4 64	26	37	37	< 0 05	
5 Hyperthyroid	4 5 64	82	76	75	1 94	
6 Hyperthyroid	8 6 64	61	60	68	0 13	
7 Euthyroid anxiety state	6 11 63		27			
8 Euthyroid six months pregnant exophthalmic ophthalmoplegia	27 1 64	20	31		< 0 05	12
9 Euthyroid boy 8 years anorexia & nervousness	10 2 64		16			20
10 Euthyroid breast feeding her baby	27 4 64		43			16
11 Hyperthyroid	8 6 64	82	82			22

is x ± Aσ, with the probability of making a false diagnosis with this limit shown as P, the percentage overlap As the peak uptake has been a major factor in the grouping of the patients, P cannot be used to compare the discriminating power of the thyroid uptake measurements and the retention values BRINKLEY et coll (1957) showed that if the diagnosis is based entirely on clinical follow up studies, the probability of a false diagnosis based on thyroid peak uptake is very much greater than our values of P However, P can be used to compare the relative reliability of thyroid 24 hour uptake, the peak uptake and the combined use of the peak uptake, PBI 131 and T_3 tests Also the relative reliability of R 24, R 48 and R 96 can be compared

From Table 2, the 24 hour thyroid uptake is just as reliable an index of hyperthyroidism as the peak uptake, and the 48 hour retention is a little more reliable than the 24 hour retention The discrimination for hypothyroidism is poorer with the retention values than the thyroid uptake measurements, R 96 is a little better than R 24 and R 48

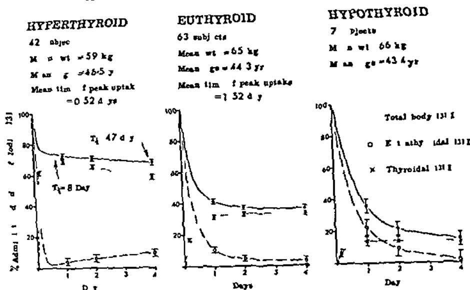


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Table 4

Standard deviation of counting — Administered dose is assumed to be 0 1 μCi ^{131}I with a 5-min scanning count

Per cent total body retention at 48 hours	Per cent standard deviation from counting statistics	Per cent total body retention at 48 hours with expected standard deviation of counting with 0 1 μCi ^{131}I and 5 min scanning
80	2 0	80 ± 1 6
60	2 4	60 ± 1 4
40	3 3	40 ± 1 3
20	5 7	20 ± 1 2
10	10 7	10 ± 1 1
5	20 4	5 ± 1 0

Background (room + subject) = 2 770 counts per 5 min scanning Subject = 63 8 counts per nanocurie ^{131}I in the thyroid per 5 min scanning

10 %, which compares with 14 % found by GOODWIN (1953) with urine collections The peak uptake occurs on average at about 12 hours after administration in hyperthyroid patients in agreement with MALAMOS et coll (1959), while in euthyroid subjects the peak is not reached until after 24 hours, this probably accounts for the slightly better discrimination with 24 hour thyroid uptake than the peak uptake measurements

The average loss in thyroidal ^{131}I in hyperthyroidism from the peak uptake to the 24 hour uptake is 3 5 % of the administered activity, with an initial average half life of 8 days, a little of this may be inorganic iodide (ROSENBERG et coll 1960) Although an average of 8 % of the administered activity is released from the thyroid by 48 hours in hyperthyroid subjects, only 3 5 % of the administered activity is lost from the body The average total body biological half life of organic iodine in hyperthyroid subjects was 47 days as taken by the tangent to the curve at 96 hours Hence the loss of thyroidal ^{131}I from the body is relatively slow even in hyperthyroid subjects, the shortest half life found was 18 days STERLING & CHODOS (1956), found the turnover rate of thyroxine to be 16 9 % per day in hyperthyroidism, but most of the liberated iodine will be reabsorbed in the thyroid, while the thyroxine excreted via the bile into the faeces is small (MYANT & POCHIN 1950, MYANT 1956)

In some patients, a 1 hour total body measurement was also made, but calibration was difficult because of the extrathyroidal iodide concentrating mechanisms of the salivary gastro enteric cycle and the kidneys, all of which play an important role in the distribution of ^{131}I at this time after administration

Table 5

Simple linear regression equation of thyroid peak uptake (Y) and the count rate in the whole body counter (X) with the crystals stationary o er the thyroid

	Per cent peak uptake (Y) as dependent variable	S_y	r	P
Simple linear regression equation	$Y = -4.0 + 1.88 \times 10 X$	8 1	0 93	< 10

r coefficient of correlation P = probability using student s t test S_y = standard error of estimate

(PIRCHER et coll. 1960, BROWN GRANT 1961 HAYS & SOLOMON 1961 ULLBERG & EWALDSSON 1964) LUSHBAUGH (1963) suggested the extrapolation of the retention to zero time as an index of thyroid activity however, unless the retention curve is extended for a prolonged length of time there will be a tendency to overestimate the thyroid uptake in euthyroid subjects

In order to confirm that the dead time corrections applied with 20 μCi ^{131}I were correct and also to see if a large reduction in administered elemental iodine changed the ^{131}I thyroid uptake due to possible extrathyroid exchange processes, eleven subjects were tested in the whole body counter with 0 1 μCi ^{131}I using the same carrier free iodine 131 from Amersham The subjects were allowed a light breakfast and were warned against ingesting high iodine content foods as before The subject s body background was determined before the ingestion of the radioiodine and the total counting time was 5 minutes consisting of 2 scans of the body Six of these subjects were retested a week later with a 20 μCi dose of ^{131}I and both total body counting and conventional thyroid uptake measurements were made The results are shown in Table 3 In cases 1 to 6 inclusive the coefficient of correlation between R 48 in both tests was $r = 0.98$ with $P < 10^{-6}$ (using the student s t/test distribution) The results of R 48 in cases 7 to 11 inclusive on 0 1 μCi ^{131}I were also clinically acceptable

It had been recommended that if carrier free ^{131}I is used for thyroid tests stable iodine 127 should be added to the stock but should not exceed one microgram of iodine (I A E A 1960) CURTIS & FERTMAN (1949) considered the optimum daily dietary intake of iodine to be about 200 micrograms However the close correlation between the 0 1 μCi and the 20 μCi ^{131}I retention values indicates that there is probably no need to add stable iodine 127 to the 0 1 μCi doses of iodine 131, although it has a very high specific activity of 20 to 30 curies per milligram of iodine and is nearly a true carrier free solution It

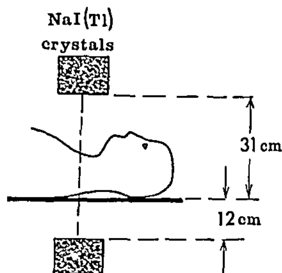


Fig. 4. Positioning of the crystals for stationary count over the thyroid centred with a perspex former midway between the laryngeal prominence and the suprasternal notch.

should be added that all patients with dentures were asked to remove them for ingestion of the iodine 131.

Table 4 gives the expected standard deviation with 0.1 μCi ^{131}I administered with different fractional body retentions. These are calculated from the counting statistics for a 5 min scanning count and do not include the errors of the method. It can be seen that these errors are less than $\pm$ 2 % of the administered dose, i.e. they are small compared with the probable errors of the method.

Fixed crystals technique

A very complete review of conventional ^{131}I uptake measurements has been done by BRUCER (1959). With specially sensitive Geiger Muller counters or NaI(Tl) crystals, doses of 1.0 μCi ^{131}I can be employed without a low background room (MORTON et coll. 1951). Using NaI(Tl) crystals very close to the thyroid burdens of 20 picocuries ^{131}I may be measured with a 30 min count for radiological protection work (LAURER et coll. 1963), and a more accurate estimate of thyroid uptake has been done with doses of 0.1 μCi of iodine 131 and iodine 125 to obtain the effective depth of the thyroid (VAN DILLA et coll. 1964). However, both these techniques are unsuitable for routine clinical use. With our two uncollimated crystals stationary and opposing through the thyroid as shown in Fig. 4, the sensitivity of evenly distributed iodine 131 in the whole body phantom was 16 % of the sensitivity of ^{131}I in the thyroid. This together with the close correlation of peak uptake and the 24 hour uptake and the small amount of extrathyroidal ^{131}I at 24 hours in hyperthyroid and euthyroid subjects, encouraged the investigation of the correlation of count

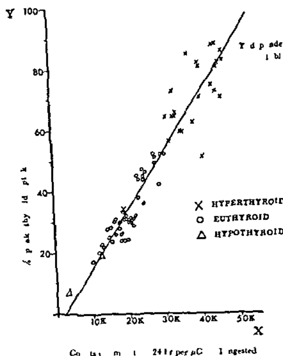


Fig 5 Scatter diagram show ng correlation between count rate at 24 hours with crystals st tionary o er the thy oid and thyro d peak uptake The mple linear correlation equation is g ven in Table 5

rate at 24 hours using the uncollimated crystals stationary and opposed through the thyroid with the peak uptake

Method Positioning of the crystals was obtained by using a perspex former and centering the crystals midway between the laryngeal prominence and the suprasternal notch There was only a 2 % variation in the sensitivity of a 20 g and 85 g thyroid in a wax phantom also, there was only a 2 % variation as the sagittal neck diameter changed from 10 to 14 cm The sensitivity of this method was 55 2 counts/min/nanocurie iodine 131 in the thyroid and with a dose of 20 μCi ^{131}I a dead time correction of up to 8 % was required Only a one minute count was necessary The contribution of counts from the body could have been reduced by using 1 cm thick lead shielding around the crystals however as most total body counters are designed without lead collimation it was considered part of the interest of the investigation to see whether this was necessary for the diagnosis of hyperthyroidism

Table 6

Expected increase in the predicted 24 hour thyroid uptake and standard deviation of the counts using 0 02 μCi ^{131}I and a 5 min count

Per cent true 24 hour thyroid uptake	Per cent possible extrathyroidal iodine 131	Estimate of uptake with un collimated crystals
80	5	81 ± 1 6
60	5	61 ± 1 4
40	10	42 ± 1 1
20	15	22 ± 0 8
10	25	14 ± 0 5

Background (room + subject) = 2 660 counts/5 min thyroid sensitivity = 276 counts/nanocurie/5 min extrathyroidal sensitivity = 44 counts/nonocurie/5 min

Eighty-one patients attending for routine iodine 131 thyroid uptake measurements were also counted in the total body counter at 24 hours with the crystals stationary over the thyroid Some of the patients were also involved in the previous investigation, and they were all given 20 μCi of ^{131}I under the same conditions, and had the PBI-131 and sometimes the T_3 measurements as before

Results

The results are shown in Fig 5 and Table 5 the coefficient of simple linear correlation r = 0 93, and the probability $P < 10^{-6}$ The thyroid peak uptake can be derived from the count rate shown in Fig 5, using the peak uptake as the dependent variable

Table 6 shows the probable contribution to the counts from the body with various 24 hour thyroid uptakes For hyperthyroid and euthyroid subjects the contribution is very small, but for hypothyroid subjects the contribution is large enough to prevent this technique from being discriminating for hypothyroidism This table also gives the standard deviation to be expected from the counting statistics using 0 02 μCi ^{131}I and a 5 min count These errors are less than ± 2 % of the administered dose in each example

Discussion

From both these investigations it is clear that very small doses of iodine 131 can be reliably used for a discriminating test between hyperthyroid and euthyroid adult subjects with the aid of two large uncollimated crystals and a low background steel room, using either a scanning technique or stationary

crystals These techniques are not very discriminating for hypothyroidism, largely due to the low renal clearance of iodide which both increases the extrathyroidal iodine 131 and also results in a higher peak uptake in the thyroid Some improvement may be obtained by prolonging the period of study for hypothyroidism

An advantage of the scanning technique is that it is self calibrating once the ratio of stomach to thyroid sensitivity has been determined It may also have advantages for patients where the thyroid is retrosternal The fixed crystal technique had the advantage of greater sensitivity but requires careful calibration

The scanning technique should be particularly suitable for small children and babies where calibration with a conventional thyroid measurement is difficult The correction factor for body shielding must be modified Experiments with phantoms have indicated that the factor varies directly but slowly with the bodyweight, down to about 10 kg, and then more rapidly approaches unity as the bodyweight approaches zero This factor can be interpolated without introducing an unacceptable error

The standard errors of estimate for both techniques are of the order of $\pm 8\%$ of the administered dose However the true standard deviation of these techniques is smaller than the calculated standard error of estimate as the random error of the thyroid uptake measurements contributes to the standard error of estimate The standard deviation for the conventional thyroid uptake measurements and the two whole body counter techniques are probably of the order of $\pm 6\%$ of the administered dose

Patients reactions to being confined in a steel room vary but only a small number are unduly concerned and only two from approximately 150 patients refused to be shut in the room A great deal of importance must be attached to the approach of the nursing staff a simple explanation of the necessity of the steel room the assurance given by a lead glass window and a push button alarm bell a radio playing and a light interior décor all do much to calm the more anxious patient A true claustrophobic could not be shut in the steel room with any amount of camouflage, without heavy sedation Two claustrophobics who were shut in the room were perfectly composed until the doors were shut but then they gave no thought to the alarm bell and tried desperately to open the doors from within It is clearly important that a watchful eye should be kept for these subjects although they are very few in number

The use of thyroid uptake tests has probably been disappointing in their ability to distinguish borderline hyperthyroid subjects for frequently the most difficult clinical picture also presents a borderline thyroid uptake measurement

The thyroid uptake depends to a large extent on renal clearance, which varies from subject to subject (MYANT et coll 1950) In hyperthyroid subjects the renal clearance is elevated and the thyroid uptake will not fully indicate the increased thyroidal clearance

The use of less than 1 μCi ^{131}I excludes the measurement of PBI 131, however, this test is highly dependent on the size of the thyroidal iodine pool, and reduction in the size of this pool often occurs in just the cases where additional confirmation is required, e g after radioiodine therapy, after partial thyroidectomy and in autoimmune thyroiditis (DONIACH & HUDSON 1957, WAYNE, KOUTRAS & ALEXANDER 1964) BRINKLEY et coll (1957) found only a small improvement in discrimination by using PBI 131 as well as thyroid peak uptake In the first investigation reported in this paper, the use of 55 % peak uptake as the upper limit of normal gave 3 1 % false positives and 5 7 % false negatives, basing the diagnosis on peak uptake and PBI-131 measurements, which indicates that the PBI-131 does not give very much extra useful information

FRASER (1956) suggested that the combination of B M R , PBI 127 and peak uptake would supply the most discriminating information Both plasma protein bound iodine (PBI-127) (BLACKBURN et coll 1955) and plasma butanol extractable iodine (BEI-127) (POSNER 1961) are useful tests particularly in mild hypothyroid subjects, although they are not necessarily an index of hormonal activity as the level of binding proteins affect the hormone transfer (ROBBINS & RALL 1960) The BEI 127 has the advantage of representing only the iodine of the thyroxine like compounds BEI-127 values for infants have been given by MAN et coll (1952) and PBI-127 values for infants by DANOWSKI et coll (1951) Hence it is suggested that adequate additional information to the peak uptake could be supplied without using radioactive techniques

The amount of iodine 131 impurity in iodine 132, obtained from sodium tellurite absorbed on an alumina column, depends on the age and frequency of milking We have found that over a 14 day period from the date of dispatch from Amersham, the iodine 131 can vary from 0 2 to 2 0 % of the activity of the iodine 132 These ^{131}I activities are of the same order as those required for thyroid studies in a whole body counter Average background radiation is approximately 3 millirad/11 day period, and the average dose to the thyroid from 0 1 μCi ^{131} I administered, in euthyroid subjects, is approximately 160 millirad over an 11 day mean time, while 20 μCi ^{132}I administered gives an average of 920 millirad over a mean time of about 4 hours

The possibility of obtaining evidence of a threshold level of radiological damage is getting more remote, as there is a consistent accumulation of evidence that somatic and genetic damage occurs at very low dose rates Such is the

lack of adequate knowledge in this important field that the major recommendations for occupational exposure are based largely on judgement and the practicality of reducing radiological exposure Even background radiation must be considered as incurring a definite statistical hazard, small for the individual but prominent for a large population (cf 'Hazards to man of nuclear and allied radiations Reports to the Medical Research Council 1956 and 1960 LEWIS 1957, WALLACE & DOBZHANSKY 1960)

There is much evidence of detrimental effects of radiation at high dose rates, and we must assume that the same effects are applicable at lower dose rates although the statistical risks to the individual are reduced and repair processes may improve the situation Evidence of the induction of papillary and follicular carcinomas and benign adenomas have been reported in the rat thyroid after administration of iodine 131 (DONIACH 1953 POTTER et coll 1960) Also there can be no sharp distinction between benign and malignant tumours in the thyroid (WILLIS 1960) External irradiation of the thyroid produces a certain risk of subsequent development of malignant tumours and the thyroid of infants and children is known to be more sensitive to radiation than the adult thyroid (see p 961 Brit. med J Vol 2 (1958) BEACH & DOLPHIN 1962) The probability of inducing leukaemia by iodine 131 is small but cannot be ignored (COURT BROWN & DOLL 1957 POCHIN 1960 HEYSSEL et coll 1960 LEWALLEN & GODWIN 1963) Chromosome abnormalities have been observed in peripheral leukocytes after ^{131}I therapy for hyperthyroidism (NOFAL & BEIERWALTES 1964)

An important aspect of this problem is the difficulty of assessing the radiation dosage to the thyroid from ^{131}I as the inhomogeneity of radioiodine in the thyroid will produce high spots of dosage There is inhomogeneity in the specific activity of ^{131}I in the thyroid as part of the thyroidal iodine pool turns over more rapidly than the rest (TRIANTAPHYLLIDIS 1958) The average thyroid size in children is smaller than in the adult (HALNAN 1964) but the mean uptake in normal children is the same as in adults (OLIVER et coll 1957) Iodine may be concentrated in the mammalian ovary particularly during the phase of follicular development (BROWN GRANT 1961) A large fraction of radioiodine can be excreted in the milk of the lactating mother (MILLER & WEETCH 1955 HALL & MYANT 1956 POTTER et coll 1959 GROSVENOR 1960) These factors indicate particular caution in women of child bearing age and children

Out of 112 patients in the first investigation 63 were euthyroid MALAMOS et coll (1959) describes thyroid tests on 1 000 subjects of which 492 were euthyroid The incidence of anxiety states and probably the incidence of hyperthyroidism associated with earlier mental stress is likely to increase as the pace of life continues to quicken This will mean an increase in the demand to

discriminate between anxiety states and hyperthyroidism, and hence an increase in the demand for iodine 131 tests

All these considerations should encourage a reduction of radiation exposure that does not involve a restriction of important clinical information to the individual

Acknowledgements

I should like to give my warm thanks to Professor J S Mitchell for suggesting the investigation and for his encouragement and help in the preparation of this paper I wish to thank all the staff of the Radiotherapeutic Centre Addenbrooke s Hospital for their collaboration In particular Dr K Duncan Miss Charlotte Spicker and Miss Wendy Briars for their careful thyroid uptake measurements Mr K I Szaz for discussions and the T_3 measurements, Mr J L Haybittle for planning the installation of the whole body counter and his helpful advice in the preparation of this paper Mrs Nancy Lane for her invaluable assistance in the handling of the patients and also the Extra Mural Research Section of the UKAEA for permanent loan of the whole body counter and the M R C for financial assistance I wish also to thank Mr R H W Sherwood Mr D A Juett and Mr P Ward for their great help and advice with the electronics

SUMMARY

With the aid of a whole body counter and a low background steel room a discriminating test for hyperthyroidism in adults may be performed with 0 1 μCi iodine 131 using the total body retention at 48 hours as an index of thyroid function It is suggested that reduction of the administered dose is desirable in many patients particularly with the increasing use of iodine 131 for routine tests in subjects most susceptible to radiological hazards

ZUSAMMENFASSUNG

Mit Hilfe eines Ganzkorperzahlers und bei Anwendung einer Spezialkammer aus Stahl um Hintergrund Strahlung zu vermindern kann ein Unterscheidungstest für Hyperthyreoidismus an Erwachsenen mit 0 1 μCi ^{131}J gemacht werden Die Gesamtkorperretention bei 48 Stunden wurde als der Index fur die Funktion der Thyreoidea angewendet Die Verminderung der Dosis ist bei vielen Patienten wünschenswert nachdem ^{131}J haufiger zu Routine Untersuchungen verwendet wird und bei sehr empfindlichen Patienten zu Rontgenschaden fuhren kann

RÉSUMÉ

La rétention corporelle totale à 48 heures considérée comme indice de la fonction thyroidienne et mesurée grace à un compteur total pour l homme et à une chambre en acier à faible mouvement propre permet de faire une épreuve de discrimination de l hyperthyroidie chez l adulte avec 0 1 μCi de ^{131}I L auteur pense qu il est souhaitable de réduire la dose administrée à de nombreux malades en particulier en raison de l emploi croissant de ^{131}I pour des examens systématiques chez des sujets très sensibles aux dangers des radiations

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SUMMARY

With the aid of a whole body counter and a low background steel room, a discriminating test for hyperthyroidism in adults may be performed with 0.1 μCi iodine 131 using the total body retention at 48 hours as an index of thyroid function. It is suggested that reduction of the administered dose is desirable in many patients, particularly with the increasing use of iodine 131 for routine tests in subjects most susceptible to radiological hazards.

ZUSAMMENFASSUNG

Mit Hilfe eines Ganzkorperzahlers und bei Anwendung einer Spezialkammer aus Stahl um Hintergrund Strahlung zu vermindern kann ein Unterscheidungstest fur Hyperthyreoidismus an Erwachsenen mit 0.1 μCi ^{131}J gemacht werden. Die Gesamtkorperretention bei 48 Stunden wurde als der Index fur die Funktion der Thyreoidea angewendet. Die Verminderung der Dosis ist bei vielen Patienten wunschenswert, nachdem ^{131}J haufiger zu Routine-Untersuchungen verwendet wird und bei sehr empfindlichen Patienten zu Rontgenschaden fuhren kann.

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FROM THE DEPARTMENT OF INTERNAL MEDICINE AND THE KING GUSTAF V RESEARCH INSTITUTE, KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN

CLINICAL WHOLE BODY COUNTING

Whole body scanner with two crystals

by

PETER REIZENSTEIN and HANS ÅKE KARLSSON

The value of whole body counting in biologic research is well established and has been reviewed in *Whole body counting* (1962) *Radioactivity in man* (1960 and 1964) and by REIZENSTEIN (1963) Initially, sodium iodide whole body counters were mainly used for investigating the quantity and the nature of radioactive contaminants in the human body in, for instance the case of persons working with radioactive materials or victims of radioactive fall out These counters were therefore designed at departments of radio physics and at atomic energy institutions where most of them are still to be found

SIEVERT'S pioneer work on natural body radioactivity was later repeated, his findings confirmed and studies of tracer metabolism commenced The value of this new instrument is now recognized in this field as well

The counter described in what follows was designed with the purpose of making whole body counting available for the purely clinical studies of tracer metabolism where it is desirable to study even very ill subjects A

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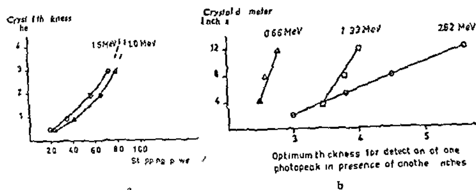


Fig 3 a) Selection of crystal size I variation of stopping power with crystal thickness (MILLER) b) Selection of crystal size II variation of crystal thickness with crystal diameter to obtain maximum energy resolution (MAY)

1 A clinical counter should be located so as to be accessible for all the patients in a large hospital so that measurements can be perfo med even on gravely ill patients with for example bandages and *intravenous drips*

2 A clinical counter should be arranged so that the expensive low background area ins de the background shield can be utilized not only for whole-body measurements but also for measurements of individual organs and for *extremely low activity samples of blood or tissues*

3 The sensitiv ty of the counter should be high enough to enable body potassium measurements to be *made* within a short time the energy resolution high enough for multiple tracer stud es and the electronic resolution time such that doses of several μCi can be measured *To meet these requirements* both solid sodium iodide and liqu d scintillation detectors were found to be necessary With such a combination *however the demands of energy resolution* on the liquid scintillation detector and the demands of sensitivity on the sod um iod de detector can be reduced

4 *In contrast to* counters used in for example fall out studies clinical whole body counters are rarely used for the identification of unknown *isotopes and expensive* analyzers with several hundred channels are rarely required for multiple tracer examinations a few channels usually sufficing

5 During the period covered by a clinical examination of tracer *metabolism there is usually a* redistribution of the isotope within the body It is therefore necessary for the counter to be as far as possible independent of the variations in geometry due to such changes

6 If it should prove that whole body counters can be of value in routine clinical diagnosis it would be necessary to develop instruments simple and inexpensive enough for use in general hospitals

This report deals with the first part of the counter, namely the background shield and the two-crystal scanning detector and its instrumentation

Background shield The premises are centrally situated in the basement floor of the hospital near the liftshaft and the corridors between the Department of Medicine and the rest of the 2 000 bed hospital (Fig 1)

In order to reduce the background activity, a base block 50 cm thick was cast in a newly discovered mineral, hoforsite (LINDELL & REIZENSTEIN) with a very low activity compared with other building materials on this a

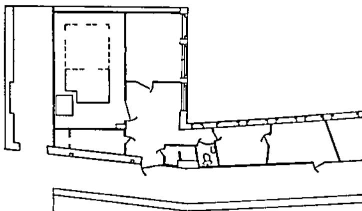


Fig 1 Plan of whole body counting laboratory Rooms left to right are counting room (top) isotope administration room (bottom) electronic workshop (top) waiting room (bottom), shower two isotope dilution laboratories

further aim was to ascertain the value of whole body counting in clinical routine diagnosis

Such a clinical whole body counter resembles in general the previous instruments designed primarily for medico physical investigations but the requirements placed on the two types of instrument differ in the following respects

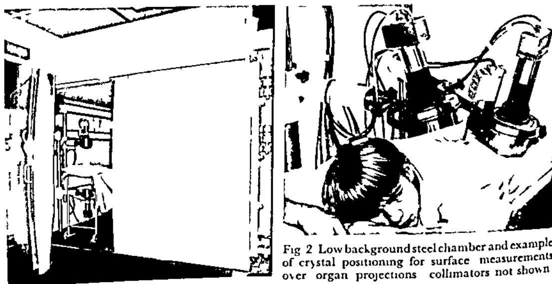


Fig 2 Low background steel chamber and example of crystal positioning for surface measurements over organ projections collimators not shown

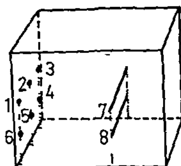


Fig 5 Magnitude of magnetic fields measured in three directions (horizontal positions parallel with door and parallel with wall and vertical position) at the numbered points in the iron chamber

immediate proximity of certain plates The field obtained at various positions in the steel room was measured and is shown in Fig 5 and Table I

The influence of magnetic fields on a RCA 8054 photomultiplier tube was also studied (in collaboration with the Royal Institute of Technology in Stockholm, thanks to Mr Wilner and Mr Naslund) The photomultiplier was placed in a homogeneous magnetic field and the shift of the 1 17 MeV ^{60}Co peak was studied In a field of 1 8 gauss the shift is 50 keV with 2 6 gauss it is 100 keV and with 5 0 gauss the shift is about 220 keV The displacement of the peak in a field of 5 gauss produced a 2 per cent reduction in the integral activity This is in agreement with the manufacturer s (RCA) statement that these tubes are affected by a field of 1 gauss which is the field obtained at about 20 cm distance from the most magnetic plates (Fig 5, Table I)

Table I

Magnetic fields in the steel room measured in three directions horizontal position parallel with door (H_D) horizontal position parallel with wall (H_W) and vertical position (V) numbered points refer to Fig 5

	H_D gauss	H_W gauss	V gauss
Point 1	0 6	0 3	1 2
2	0 1	0 3	0 2
3	0 2	0 8	0 7
4	0 1	0 6	0 3
5	0 1	0 2	0 3
6	1 0	0 1	0 9
Line 1	<0 6	<0 7	<0 4
2	<0 2	<0 6	<0 2

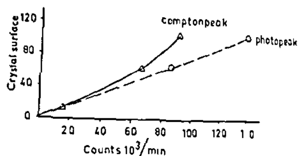


Fig. 4. Selection of crystal size III: variation of crystal surface (sq. in.) in relation to efficiency (cps × 10^3)

chamber (Fig. 2a) of 150 mm armour steel composed of 15 blocks welded externally with stainless Bohler electrodes (type FOX EAS 4 M A) was constructed. The chamber measures 270 × 205 × 200 cm and the doors each weigh 5 500 kg and are hinged on 6 SKF ballbearings. The chamber is lined with 3 mm soft sheet lead, Bolidens B lead. A large container (301 × 218 × 25 cm) for possible borax screening of cosmic neutrons is situated on the top of the chamber. The latter is ventilated, to avoid radon accumulation, with an arrangement that gives about 250 m³ air per hour, and a constant temperature.

Detectors. Two Harshaw sodium iodide (Tl) crystals, 5 inches in diameter and 3 inches thick (about 77 × 127 mm), are used for the measurements (Fig. 2b). These dimensions were chosen for the following reasons. There is no appreciable increase in stopping power for a thickness of more than 3 inches (Fig. 3a), and since the cost is proportional to the volume a reduction from the conventional 4 inches of thickness to 3 inches represents a 25 per cent saving.

The optimal thickness for the detection of one photopeak in the presence of another is about 3.5 inches for a 5 inch crystal for measurements in the energy interval where most clinically used tracers are found (under or around 1.3 MeV) (Fig. 3b). However, the resolution obtained with a 3 inch thick crystal (9.5 to 10 per cent) is satisfactory for clinical purposes and multiple tracer studies. Efficiency is approximately proportional to the flat crystal surface (Fig. 4). Two 5 inch crystals have the same efficiency as a single conventional 8 × 4 inch crystal but are preferable from the point of geometry independence. Two 5 × 3 inch crystals were therefore selected.

Magnetic fields.[1] Magnetic fields surrounding the pieces of armour plate, which had been stored in approximately a north south direction and apparently lifted with non magnetic cranes, were measured both before and after the construction of the room. Maximum activities of 6 gauss were found in the

Table 2

Performance for low activity sample counts and whole body counts — Background and sample or patient respectively measured for 1000 sec each

	Low activity sample	Whole-body count
Background (without sample/patient)	26 4 cps	28.7cps
Effic ency (Fe)	40 1 %	0 9
Precision (QUIMBY et coll)	0 015 × 10 Ci	0 7 × 10 Ci
Minimum measurable activity (for statistical error 5)	0 280 × 10 Ci	15 × 10 Ci

The photomutiplier tubes, in extreme scanning positions, are 18 cm distant from the steel room wall Small differences between moving and stationary crystals may accordingly be obtained in integral counts for background meas urements If higher activities are measured by moving a preparation in parallel with the crystals no difference between moving and stationary meas urements is evident

Scanning device Scanning is performed along a longitudinal axis with crystals under and above the body of the subject lying on a stretcher A single crystal scanning counter was recently described by CEDERQUIST (1964) The rate at which the crystals scan the body can be regulated between 180 and 1 100 seconds for a single scanning The driving device consists of two carriages with vertical shafts on each of which one crystal holder is mounted

The carriages are moved by screws driven by an electrical motor mounted on the back and outside of the chamber The speed is regulated with the aid of a variator The use of microswitches that change the direction of the variator or stop the motor at the end points, renders the scanning automatic The patient himself can stop the crystals by means of a control in the chamber A pendulum in front of the upper crystal breaks the current and arrests the crystals if the patient should accidentally sit up or if anything should touch them

The crystals may be moved in the vertical and lateral directions as well as rotated through any desired angle Each movable part is provided with a scale graduated in degrees or millimeters to enable the settings to be reproduced (Fig 6) Measurements with stationary crystals may be made with crystals over any part of the body, or the crystals may be used to measure samples Extreme limits of crystal positions are shown in Fig 7

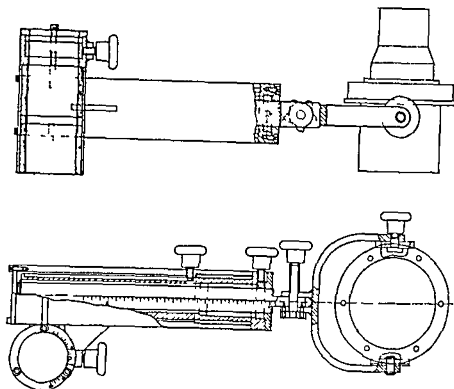


Fig 6 Crystal holder

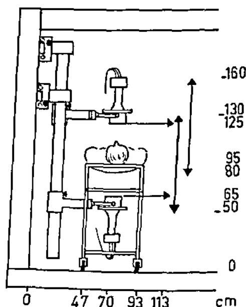
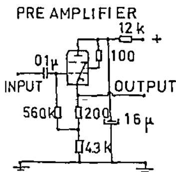
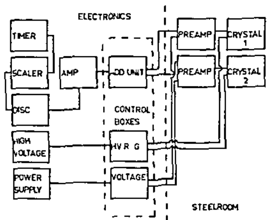


Fig 7 View of patient lying between detectors Figures indicate crystal distances to patient walls and floor and patient's position The arrows show extreme crystal positions the right vertical arrow points to the top crystal and the left one to the bottom crystal



F g 9 Preampl fier



F g 10 Block schematic electronic system

	INTEGRAL CO T re One-channel ystem 0 1–2 MeV
Initial alue	1 00
Aft casting H f rsit bed	1248
laying floor	1133
doo recting alls	426
fitting doors and roof	77
pplsing l ad overing	18
installing ve tilation	17

F g 11 Background reduct on.

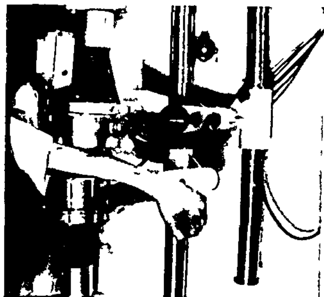


Fig 8 Arm measurements Device to standardize arm position not shown

Technique of measurements

Total body scanning The top crystal is usually 40 cm and the bottom crystal 20 cm from the back of the patient (Fig 7) Under these conditions, and when background and patient alike are measured for 1 000 seconds each, the standard deviation due to the random nature of the counts in a single measurement of natural human radioactivity (24 nCi, ^{40}K and ^{137}Cs) is 2 to 2 5 % for an integral count In the 1 2 to 1 7 MeV range where only ^{40}K but not ^{137}Cs is measured, the error is about 5 % if the patient is measured for 2 000 seconds and the background for 30 000 seconds

Plasma clearance and circulation studies are attempted by using arm measurements, where the arm is placed between the crystals through a hole in the shield (Fig 8)

Low activity sample measurements are performed with a 43 cm^3 sample holder, spreading the sample in a 3 mm layer over the crystal surface as previously described (REIZENSTEIN CRONKITE & COHN) By setting one crystal over and the other under the holder, a geometric efficiency approaching 100 per cent is reached The sample holder is filled through one of the funnels, the other being left open to allow air to escape Total efficiency and precision is shown in Table 2

For *organ measurements* (liver, kidney, thyroid, see Fig 2b) no routine procedures have yet been developed

Various errors are analyzed in Table 3 As an example of the important errors due to isotopic redistribution, the efficiency variation after oral ^{59}Fe administration was analyzed The same analysis has previously been made for a single stationary crystal counter (LINDELL, REIZENSTEIN & STRANDBERG), and the errors are compared (Table 3) It can be seen that these errors which are a major limitation in for instance, measurements of intestinal absorption could be reduced between three and seven fold with the two-crystal scanning device

Acknowledgements

This work was supported by the Ericsson Foundation Folksam Insurance Co and the Swedish Medical and Technical Research Councils Valuable help in the design and building was given by the engineers Westerlund Kervefors and Soderlund The armour plate was loaned by Kungl Fortifikationsförvaltningen and Karlskronavarvet. The help given by Hospital Director G Karlen and Professors H Lagerlof and G Birke is gratefully acknowledged

SUMMARY

The background shield and the two-crystal scanning detector of a clinical whole body counter are described and differences in the requirements of biophysical and clinical counters are discussed

ZUSAMMENFASSUNG

Ein Hintergrundschild und ein mit 2 Kristallen ausgerusteter Scanning Detector zur Zahlung der Totalkorperbestrahlung werden beschrieben Die verschiedenen Anforderungen fur die biophysikalischen und klinischen Zahler werden erortet.

RÉSUMÉ

Description de la protection contre le bruit de fond et du détecteur a deux cristaux d un compteur corporel total utilisable en clinique Discussion des différences de spécifications entre les compteurs biophysiques et les compteurs cliniques

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Table 3

Errors in two-crystal scanning counter as compared with those in a single stationary crystal whole body counter

Type of error	Number of measurements	Method of calculation	Magnitude of error in % of total count: Two-crystal scanning counter	Single stationary crystal counter*: 35 cm**	Single stationary crystal counter*: 60 cm**
Background variation					
Without ventilation (1 000 sec measurem.)	20	S D	4 1	—	—
With ventilation	42	S D	1 1	—	—
Expected statistical variation of background			0 6		
Error in patient position (σ_p)	22	S D $\times 2^{-1/2}$	1 2	4 4	3 6
Total variation 1st hour after oral administration	16	S D	4 0	30	11
Total variation 2nd 24th hour (σ_q)	16	S D	2 5	13	9 4
Variation due only to redistribution 2nd 24th hour after oral administration (σ_m)***	16		2 2	—	—

* LINDELL REIZENSTEIN & STRANDBERG

** Distance from the crystal to the patient s back

*** $\sigma_m = \sqrt{\sigma_q^2 - \sigma_p^2 - \sigma_s^2}$ where σ_s is the statistical variation due to random nature of radioactive disintegration

Electronics and performance The pulses pass from the 3 inch RCA 8054 photomultiplier tubes through a short coaxial cable to a valve preamplifier (Fig 9) The recording equipment consists of a main pulse amplifier that can be regulated so that the pulse height analyzer passes the pulses within the required energy interval Two energy channels may be measured simultaneously, or one used for each crystal The counts are recorded on a visual Ekco scaler

A schematic block electronic system is shown in Fig 10 This simple and inexpensive equipment has been found to suffice so far for all clinical measurements

The background within the shield is about 1 per cent of the unshielded background (Fig 11), or 28 cps in the 0 1 to 2 MeV energy interval The efficiency for ^{59}Fe in the human body 5 minutes after oral administration is 0 9 per cent

FROM THE DEPARTMENTS OF RADIOTHERAPY AND PHYSICAL MEDICINE LUND
UNIVERSITY HOSPITAL SWEDEN

ELECTROMYOGRAPHIC CHANGES FOLLOWING ROENTGEN TREATMENT OF THE PAINFUL SHOULDER SYNDROME

by

C. H. Hakansson and U. Moritz

The painful shoulder syndrome is a blanket name used to designate a wide range of painful conditions of the shoulder irrespective of their pathogenesis. The syndrome embraces rheumatoid diseases, tendinitis with or without calcification, bursitis, osteoarthritis and certain types of cervical root compression. In most of these conditions radiotherapy, formerly with radium (Hogler 1928) but since 1930 with roentgen rays, has proved useful in the alleviation of the pain. This beneficial effect of roentgen treatment constitutes our basis for the treatment of painful shoulders, our knowledge of the intricate effect of the irradiation itself being founded on theoretical deductions.

The deltoid muscle was examined electromyographically in patients referred for roentgen treatment of painful shoulders to investigate further the effect of irradiation on the electrical phenomena of the tissues. In the abundant literature on the painful shoulder syndrome interest has been focused upon

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Potential duration in msec						
Clinically affected shoulder			Non or less affected shoulder			Normal value
1st exam	2nd exam	3rd exam	1st exam	2nd exam	3rd exam	
8 7	10 4		11 2	10 8		13 0
11 0	12 4	9 1	11 7	12 1	10 6	14 1
7 9	7 9	9 0	7 8	6 6	8 9	13 8
9 1			14 2			13 4
11 0	12 7		10 3	11 7		13 8
10 5	10 6	11 7	12 7	11 5	11 2	15 3
11 6	13 0	11 5	11 6	13 0	10 6	14 8
13 6			12 4			14 4
11 2			11 5			14 2
9 7	10 6	13 1	12 1	11 7	12 4	13 8
11 6			11 7			14 5
11 6			13 0			14 7
10 0	11 1		12 1	8 3		14 1
10 9			13 6			13 5
9 1			12 1			14 2
11 1	11 2		10 9	11 7		14 4
12 4						15 0
10 6	11 3	12 2	13 6	14 2	13 5	14 1
15 3	14 1		13 7			14 8
14 5			11 9			14 5
11 8	12 0	11 9	10 8	10 0	11 0	14 1
8.8	9 3	14 0	7 9	7 7	11 5	14 7
10 5	11 5	12 9	12 1	12 1	13 6	14 5
11 4			11 1			12 1
10 5			12 3			12 9
9 3			12 0			

Table 1

Mean action potential duration in deltoid muscles from patients with painful shoulder syndrome

Cases	Age	Diagnosis		Duration of symptoms	Roentgen findings
1 S M	35	*Periarthritis* humeroscapul	sin	*3 days*	*Ca deposits* L shoulder
2 H N	53	»	sin	1 week	Ca deposits L shoulder
3 E H	48	»	sin	2 weeks	Ca deposits L shoulder
4 E N	41	»	dx	1 1/2 months	Ca deposits R shoulder
5 S L	49	»	amb	4 months	Ca deposits R shoulder
6 K O	74	»	dx	5 days	Normal
7 K E	66	»	amb	1 month	Normal
8 R Å	58	»	dx	2 months	Osteoporosis
9 M W	55	»	amb	2 months	n d
10 E A	49	»	amb	2 months	Normal
11 A L	60	»	*sin*	2 months	Normal
12 O N	63	»	amb	2 months	Osteoarthr
13 E L	53	»	dx	3 months	Normal
14 G S	44	»	sin	3 months	n d
15 G W	54	»	sin	3 months	Osteoarthr
16 I S	58	»	amb	3 months	Osteoarthr
17 K J	70	»	dx	8 months	*Osteoarthr*
18 E J	53	»	dx	1 year	Osteoarthr
19 E H	65	Rhizopathia cervicalis		6 weeks	Normal
20 A H	61	»		6 years	Normal
21 O J	53	Spondylarthr ankylopoet		3 months	Arthr changes
22 F L	63	Arthr rheumatoides		4 months	Arthr changes
23 N H	61	»		11 months	Arthr changes
24 E O	19	Lymphogranul maligna + Periarthr humeroscapul	dx	1 week	Ca deposits R shoulder
25 G N	33	Tumor cerebri Periarthr humeroscapul	dx	3 months	Osteo porosis

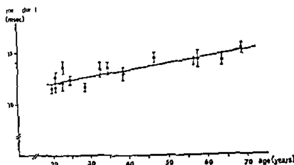


Fig 1 Mean durations of motor unit potentials from the deltoid muscle in 16 controls Verticals indicate individual standard error of the mean

of the body naked In 5 patients, measurements were made of the temperature of the skin subcutaneous tissue and deltoid muscle, and in one patient undergoing treatment for osteoarthritis of the spine, the temperature was measured in the region of the trapezius Measurements in these patients were carried out before and after roentgen treatment, the intramuscular temperature in 5 other patients was measured before treatment only

Material The control material consisted of electromyograms of 16 deltoid muscles in 13 subjects without clinical evidence or history of neuromuscular disease (10 healthy patients 2 with bronchial asthma and 1 patient with osteoarthritis of the spine) and in 3 patients with traumatic nerve lesions on the opposite side The ages ranged from 20 to 69 years (mean 37 years) The controls were selected irrespective of sex since it has been shown (BUCHTHAL, PINELLI & ROSENFALCK 1954) that there is no significant difference between the duration of motor unit potentials in males as compared with females

The clinical material consisted of 26 patients (13 females and 13 males) selected at random from those admitted for roentgen treatment of the painful shoulder syndrome The clinical diagnoses are given in Table 1 Fifty one deltoid muscles in all were examined The ages of the patients ranged from 19 to 74 years (mean 51 years) Symptoms and signs were unilateral in 17 patients and bilateral in the remaining 9 Nine of the patients had suffered from similar symptoms before The patients had had symptoms for 3 days to 6 years (Table 1) five of them for less than three weeks Twenty one complained of severe pain on movement Five patients had calcium deposits in the affected shoulder but none had deposits on the unaffected side Tenderness was noted in eleven patients and slight atrophy of the deltoid muscle in eight The results of roentgen examination are given in Table 1 Symptoms of other joints

calcifying tendinitis, especially of the supraspinatus tendon, and little attention has been paid to the muscles that surround the joint The joint pain is believed to emanate from the articular capsule, tendon tissue, or periosteal tendon insertion (apophysis) (SCHAER 1936)

MILONE & COPELAND (1961) published an excellent survey of calcifying tendinitis and its treatment but said nothing about any muscle changes accompanying tendinitis or periarticular disease

MULLER (1924) and DOLLINGER (1932) were among the first to describe muscle changes, 'Myogelose', in periarthritis humeroscapularis Histologic correlates to these muscle changes could not be demonstrated (LANGE 1934)

One of the known effects of irradiation is an increase of the blood flow and temperature in the irradiated part of the body Since an increase in intramuscular temperature affects the shape and duration of motor unit action potentials (BENTSEN 1945, BUCHTHAL, PINELLI & ROSENFALCK 1954), the investigation was extended to include temperature recordings in the irradiated area

Roentgen treatment The factors were 170 kV, HVL 1 mm Cu, FSD 50 cm, field size ~ 150 cm Equal total doses of 500 to 700 R were given to the ventral area and dorsal area of the deltoid region in 9 days, in fractionated doses of 100 to 200 R

Electromyography The recording instrument used was a 3 channel DISA Electromyograph (Type 13 A 69 Dansk Industrisyndikat, Copenhagen) with concentric needle electrodes Three electrodes were inserted at several sites and to different depths of the deltoid muscle on both sides The muscle was first examined at rest, and any spontaneous activity was recorded The muscle was then studied during maximal voluntary effort at low amplification (1 000 μV/cm) with continuous recording (film speed 5 cm/sec) Thereafter the activity during weak voluntary effort was recorded at high amplification (100 μV/cm) with interrupted sweeps with a sweep speed of 1 mm/msec Motor unit action potentials were sampled at random from 20 to 30 different points in each muscle The duration of the single motor unit potential was measured from the beginning of the initial deflection to the return of the terminal deflection to the base line The mean duration of 20 to 30 different motor unit potentials in each muscle was calculated Potentials with more than four phases were said to be polyphasic The examination was repeated on the last day of the roentgen treatment in 14 patients and in 10 of these one month later as well

Temperature Temperatures were recorded at room temperature (24 to 25° C) after the patient had been resting for 15 minutes with the upper part

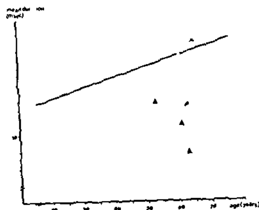


Fig 3 Mean duration of motor unit potentials from the deltoid muscle of the affected side in 26 patients with painful shoulder syndrome
● periarthritis humeroscapularis
▲ rheumatoid arthritis suspected rheumatoid spondylitis
⊗ cervical rhizopathy
▬ regression line of mean values from control subjects
2 6 × residual deviation

Activity at rest consisting of 'end plate potentials' (BUCHTHAL 1957) or repetitive discharge of triphasic short potentials, was never observed at more than one point of insertion At maximal voluntary effort all the muscles had an interference pattern (Fig 1)

Clinical material The electromyographic abnormalities most frequently found in the deltoid muscle before roentgen treatment consisted of a shortened duration of the potential and an increased frequency of polyphasic potentials (Fig 2) Such abnormalities are generally regarded to be the result of myopathy or other disorders with loss of functioning muscle fibres within the motor units

A comparison of the mean values of the motor unit potentials on the affected, the unaffected, or on the less affected side, and the normal values is presented in Table 1

The mean potential duration on the affected side was significantly reduced in 21 of the 26 patients (Fig 3) A definitely normal mean potential duration was found in the 2 patients in whom the shoulder pain was probably due to cervical root compression There was no correlation between the duration of symptoms and the electromyographic results A markedly reduced potential duration was found in one patient, who had had symptoms for 3 days only

Electromyographic examination of the opposite side revealed a decreased mean potential duration not only in patients with bilateral symptoms but also in a number of those who had symptoms on one side only at the time of examination A discrepancy between clinical and electromyographic findings was thus occasionally apparent

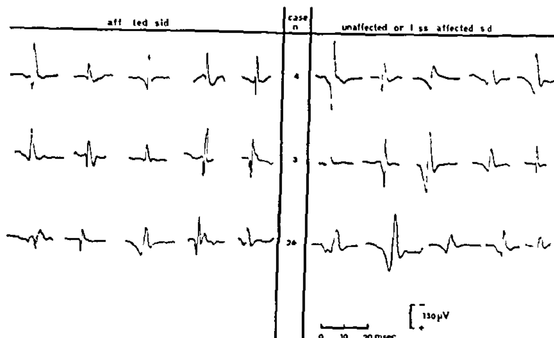


Fig 2 Motor unit action potentials recorded from both deltoid muscles in Cases 4 3 and 26 Potentials from the affected side show a reduced duration and increased irregularity

were present in five patients Decreased range of improvement and pain in the cervical spine were noted in six patients and two (Cases 19 and 20) had symptoms of cervical root compression Two patients had active rheumatoid arthritis (Cases 22, 23), and incipient rheumatoid spondylitis with involvement of the shoulder joints was considered probable in another (Case 21)

Treatment In addition to roentgen treatment the patients were given analgesic drugs One (Case 22) was receiving oral steroids Roentgen treatment had been antedated by intra articular injections of hydrocortisone without persistent effect in four patients

Results

Control material Fig 1 shows that the mean duration of the motor unit potentials increased with age (coefficient of correlation = + 0 89), it increased by approximately 20 per cent between 20 and 60 years of age (coefficient of regression = 0 058) The equation for the regression line of mean duration (in msec) = y (age in years = x) was y = 12 7 + 0 058(x − 30)

The deviation of the mean values from the line of regression averaged 0 5 msec The average standard error of the individual mean values was also 0 5 msec The inter observer error was within the limits of the error of the method

Table 2

Change in mean duration of motor unit potentials in relation to clinical results of roentgen treatment

Clinical results	Number of cases	change in duration of motor unit potentials	
		Average	Range
No effect	2	+ 5	− 1 — + 11
Slight improvement	3	+ 8	+ 1 — + 23
Marked improvement	7	+ 22	+ 1 — + 59

significantly from that of the unaffected or less affected side (mean = 36 4° C) The individual values ranged from 34 8 to 37 1° C

The skin temperature the subcutaneous temperature, and the intramuscular temperature, were measured before and after roentgen treatment in 6 patients (Fig 5) A slight elevation was noted in four patients No such increase was found on the untreated side

Discussion

The present material consisted of a random selection of patients admitted to a radiotherapeutic clinic for treatment of shoulder pain The material was pathologically inhomogenous but this was of little importance since the initial purpose of the study was to find out whether roentgen treatment has any influence on the electrophysiologic activity of muscular tissue as measured by means of electromyography At an early stage of the study it was found that many patients before treatment had a reduced potential duration and an increased number of polyphasic potentials of the deltoid muscles These electromyographic abnormalities are generally assumed to indicate an affection of the muscular tissue with random loss of functioning muscle fibres within the motor units (myopathy) (KUGELBERG 1947)

MÜLLER (1924) was one of the first to suggest that changes in the shoulder muscles play a causal role in the painful shoulder syndrome He wrote *Ich betone* dass die Muskelerkrankung das Primare bei diesem Leiden, der Hauptsitz und die Ursache der ganzen Erkrankung ist Later on, DOLLINGER (1932) again put forward the idea of muscular involvement in connection with periarthritis humeroscapularis no histologic correlates to DOLLINGER's clinical findings of Myogelosen could however be detected (LANGE 1934)

The possible role of the muscles in the painful shoulder syndrome has since

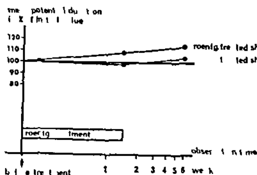


Fig 4 Changes in mean duration of potentials after roentgen treatment as percentage of initial value

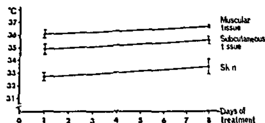


Fig 5 Results of temperature measurement before and after roentgen treatment mean values for 6 patients Verticals indicate standard error of the mean

Examination at rest disclosed an increased insertional activity and protracted electric activity consisting of short di- and triphasic potentials at more than one point of insertion in 2 patients (affected side) In the other patients activity at rest was present to the same extent as in healthy patients (MORITZ 1963) Examination of the deltoid muscle on the clinically affected side at maximal voluntary effort revealed an interference pattern in 15 patients, and a mixed pattern in 11 patients (for definition see BUCHTHAL 1957) The unaffected or less affected side had an interference pattern in 20, and a mixed pattern in 5 patients In no instance were single motor unit potentials noted in electromyograms traced during maximal effort There was a clear correlation between the decrease of interference and the severity of pain and tenderness of the shoulder joint

Re-examination after roentgen treatment revealed a tendency to a return to normal values, with an increase of the duration of the motor unit potentials (Fig 4) There was a slight final increase in potential duration even on the side not treated with roentgen radiation This was because the two patients with rheumatoid arthritis improved during the time of observation

Table 2 presents the change in potential duration after roentgen treatment in relation to the clinical results The potential duration increased by on the average 22 % in patients with marked clinical improvement against 8 % and 5 % in those in whom roentgen treatment had produced little or no improvement

Temperature recordings The temperature of the deltoid muscle on the affected side in 7 patients before roentgen treatment (mean = 36 6° C) did not differ

Irradiation in the present material was followed by an average elevation of the muscle temperature by 0.7 C. The physiologic effect of this rise should therefore be a decrease on the action potential duration, although a lengthening of the duration was actually recorded. Had a correction for temperature been made the duration would have been even longer.

The present findings indicate the existence of a correlation between clinical improvement and the degree of electromyographic normalization. It would therefore appear that this method may be useful in similar studies of the effect of other types of treatment.

SUMMARY

Twenty six patients with the painful shoulder syndrome were investigated by electromyography of the deltoid muscles. Most of the patients had signs on the affected side generally considered to be manifestations of myositis. Roentgen treatment produced an improvement in the electromyographic pattern accompanied by a corresponding improvement in the clinical condition.

ZUSAMMENFASSUNG

Elektromyographien wurden an sechs-und zwanzig Patienten mit schmerzhaftem Schultersyndrom am Deltoidmuskel vorgenommen. Die meisten Patienten hatten Symptome auf der erkrankten Seite, die auf eine Myositis zuruckgefuhrt wurden. Nach Rontgenbestrahlung zeigte sich eine Verbesserung der elektromyographischen Messungen und ebenso eine Verbesserung des klinischen Befundes.

RÉSUMÉ

Vingt six malades atteints de syndrome douloureux de l épaule ont subi un examen électromyographique des muscles deltoides. La plupart des malades présentaient du coté malade des signes considérés comme des manifestations de myosite. La roentgenthérapie a donné lieu a une amélioration du tracé électromyographique accompagnée d une amélioration clinique correspondante.

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received little attention, interest being focused on the tendons, tendon insertions, bursa subacromialis and the joint capsule, as reflected in such terms as calcifying tendinitis and subacromial bursitis.

As appears from the results presented in this paper, the painful shoulder syndrome is often associated with involvement of adjacent muscle tissue, a finding favouring the term 'periarthritis humeroscapularis' originally suggested by DUPLAY 1872.

Conventional histologic examination of muscle biopsies from a few patients revealed no definite abnormalities. The histologic basis of this reversible loss of functioning muscle fibres within several motor units is thus unknown but edema and perhaps infiltration of leuco lymphocytes similar to that occurring in the tissue around an affected joint might be the causative factors. The effect of roentgen treatment appears to support this assumption, it being known that ionizing irradiation has a favourable effect on infiltration and edema.

According to clinical experience, roentgen treatment frequently gives rapid relief of pain within 3 to 5 days. This observation has also been made by PENDERGRASS & HODES (1941). PLENK (1952), however, was of the opinion that roentgen treatment does not accelerate recovery. Unlike the rapid response of pain, the electromyographic abnormalities regress slowly over several weeks.

Pain arising from periarticular tissue may be caused by inflammatory changes with edema and cellular infiltrations. The role of the calcium deposits as the causation of pain (mostly seen in the supraspinatus tendon) is still obscure, but roentgen treatment cannot eliminate calcium deposits in so short a time as less than a week. This suggests that calcium deposits are of minor importance as pain producing agents. Histochemical studies in animals have shown that roentgen treatment is followed within a few days by an increase of the concentration of the soluble calcium salts in the irradiated tissue (MELTZER & KUHTZ 1938); this is believed to have an anti inflammatory effect. The rapid antiphlogistic action of roentgen treatment resembles that of cortisone (MEAD 1918, QUIGLEY 1957). Another effect of the irradiation is a local elevation of the temperature secondary to an active hyperaemia, which might eliminate edema and infiltration. Roentgen treatment is similar to diathermy with regard to elevation of temperature but the temperature rise after roentgen treatment is only moderate and lasts about 3 to 4 weeks (NEMENOW 1931, DAHL 1936). The influence of the temperature on the action potential duration has been investigated especially by BUCHTHAL, PINELLI & ROSENFALCK (1954); these authors found the duration in human biceps to increase with decreasing temperature. (Within the normal range of the body temperature the mean duration increased by less than 10 % per degree Celsius.)

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THE ORGANIZATION OF CLINICAL DOSIMETRY

I The four stages of clinical dosimetry

by

MONTAGUE COHEN

The purpose of this paper is to review the practical aspects of clinical dosimetry and to indicate where further research or development is needed We must begin by defining clinical dosimetry This term is the title of Report 10d of the International Commission on Radiological Units and Measurements (*ICRU 1963*) and it is interesting to note that although the report contains a large number of definitions, clinical dosimetry itself is not defined! However we cannot go far wrong in describing clinical dosimetry as dosimetry related specifically to the treatment of patients We thus exclude fundamental physical dosimetry which is concerned with the interaction of radiation with matter in general terms, including the definition and realization of dosage units the determination of the properties of radiation sources and the calibration of standard and sub standard measuring instruments This type of information may be needed for many other applications besides the treatment of patients for example in radiobiology in radiation protection and in studying the effects of radiation on the properties of solids The physicist

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a comprehensive collection of single field isodose charts for 50 cm source surface distance is available (TSIEN and COHEN 1962), comprising 50 charts for each of the half value layers 1 0, 1 5 2 0 2 5 and 3 0 mm Cu These charts are intended for closed ended applicators of a particular type (Fulfield) but instructions for using the charts with other applicators, or with open cones, are included However the charts are applicable only to 50 cm SSD and no comparable collection exists for other SSD s

For high energy radiation including the gamma rays of cobalt 60 and caesium 137 thousands of isodose charts have been measured in the past decade — certainly far too many to allow publication in a single volume The problem of supply and distribution has therefore been tackled in different ways Firstly details of over 2 600 single field charts are included in an International Guide published by the IAEA in 1962, and potential users can request copies from the originators of the data In order to facilitate this kind of exchange many of the charts (and the number is constantly increasing) are listed in the Catalogue No 1 (1964) of the Radiation Data for Medical Use scheme which is run by the International Atomic Energy Agency and these charts may be purchased at low cost direct from the Agency The scheme incorporates the former Diagrams and Data' scheme of the Hospital Physicists Association Finally an atlas containing about 160 representative single field full size charts has just been published (WEBSTER and TSIEN 1965) This atlas is not intended for direct clinical use — only three field sizes are given for each of the chosen conditions — but the material should prove valuable for reference comparison and teaching and as an aid in selecting new equipment

It must be emphasized that whenever isodose charts and other data are obtained from outside sources it is the responsibility of the individual physicist to make sure that the data are applicable to the particular equipment and conditions to be used in his own hospital

Up to this point all measurements are made by the physicist and his assistants and no collaboration is required from his medical colleagues except the essential passive co operation which the radiotherapist provides in allowing the physicist a reasonable period of time (often several weeks) to carry out the measurements before the machine is put into clinical service The only organization required is that the physicist must first persuade the radiotherapist to control his natural desire to treat patients the day after a new machine is installed and then he must get on with the measurement programme as quickly as possible In the present paper it will be assumed that all the preliminary physical measurements have been made and we will consider only what happens when the treatment of patients is planned and carried out

working in a hospital will certainly be concerned to some extent with fundamental dosimetry and probably also with applications other than clinical dosimetry, but all these fields will be excluded from the present review.

Let us go one step further. The determination of dose distributions in a homogeneous phantom, such as a tank of water, is usually considered part of clinical dosimetry since these distributions, in the form of isodose charts and tables of central axis depth dose values, are required mainly for assessing the dose in patients. This part of the hospital physicist's duties is important and is likely to occupy a substantial proportion of his time. Nevertheless we shall devote only a few introductory paragraphs to this topic.

Let us suppose that a new source of radiation, such as a roentgen or a cobalt unit, is installed in a hospital. The physicist must take the necessary steps to ensure that all physical data required for treatment are made available as soon as possible. This means that he must first check all the mechanical, physical and geometrical features of the unit which may affect its performance, for example the means of defining the source surface distance, the significance of the 'field size' as defined by the cones, collimator control knob and/or light simulator provided, and the beam alignment in relation to the collimating system.

The physicist must then determine, by direct measurement, the radiation dose rate delivered by the machine, under defined and easily reproduced conditions, i.e. the output of the unit. Standard procedures for carrying out this measurement have been described in the Codes of Practice' issued by the Hospital Physicists' Association (1960, 1964), see also MEREDITH (1963). If the output is measured in air it is necessary to determine the relationship between this value and the dose rate at a convenient reference point in a water phantom, and, in any case, the variation in the latter dose rate according to the conditions of treatment (e.g. field size, SSD, filtration) must be known, either from direct measurements or from values reported in the literature for closely similar situations.

Having determined the dose rate at a single point in a water phantom, for each combination of parameters to be used in clinical practice, the dose rates at other points are assessed by means of data on relative dose distributions, i.e. central axis depth dose data and isodose curves. The physicist has to decide whether the data of this type must be measured locally or can safely be purchased from outside. For central axis data Supplement No. 10 of the British Journal of Radiology (H.P.A. 1961) will be found to cover most situations, but the requirements for isodose charts are so varied that no single publication or collection can be expected to embrace all needs or possibilities.

For medium energy roentgen rays (the conventional 180—250 kV range)

From now on we shall refer to clinical dosimetry in this more limited sense of what happens after the equipment has been brought into clinical service

The physicist, having enjoyed full sovereignty over the roentgen or cobalt unit for several weeks must now accept the fact that he is only one of a team Clinical dosimetry is essentially a team effort and, as such, requires a certain amount of organization The individualist will find however that there is still plenty of scope for research and development

The four stages of clinical dosimetry

It is convenient to divide clinical dosimetry into four stages, which may be called topography, planning treatment and reconsideration These stages can be distinguished both in teletherapy and in therapy with small discrete sources *although the emphasis is somewhat different in the two fields*

In Table 1 the four stages are summarized, with particular reference to teletherapy In each stage the requirements are set out as minimum and optimum Neither term is strictly correct There are many clinics, in all parts of the world where patients are irradiated without even the minimum procedures stated *in the table but we should avoid calling such irradiation radio* therapy On the other hand the optimum procedures are somewhat idealistic It is doubtful if any radiotherapy centre exists in which the optimum procedure is carried through in full for every patient Nevertheless it shows what we should aim at The final column indicates the people who are likely to be involved at each stage No significance should be attached to the order in which they appear nor is any judgement implied as to the allocation of legal or other responsibility We see that at least four people, or groups of people are *involved in clinical dosimetry at one stage or another*

In stage I the extent of the tumour is determined and also its position in relation to the surface and deeper anatomy of the patient Usually this is done by ordinary radiography, combined with direct measurement of the patient s outline using calipers a lead strip or one of the many gadgets described in the literature (e g FRIEDMAN HINE & DRESNER 1955 PFALZNER & INCH 1956) There is little doubt however that a more accurate method is transverse tomography which *in any case is required if detailed* corrections for body composition are to be made We will return to this question later Meanwhile it may be noted that any method in stage I will introduce errors if the patient is measured *in one position* (e g standing up) and treated in another (e g lying down) Furthermore, during a course of treatment both the size of the tumour and the outline of the patient may change so it is advisable to re measure at least once

Table 1

Organization of clinical dosimetry

Stage	Procedure	Requirements: Minimum	Requirements: Optimum	Personnel
I	*Topography* Body contour Tumour size Tumour location	Direct measurement of body outline Palpation of tumour Radiography of tumour	Transverse tomography	Radiotherapist Radiologist
II	*Planning* Prescription	Minimum tumour dose Maximum normal tissue dose	Description of required dose distribution	Radiotherapist
	Dose planning tank of water	Dose at a few points (single plan)	Complete isodose chart plus integral dose (alternative plans)	Physicist Radiotherapist
	Dose planning actual patient	None	Full correction or *compensation for* body size body composition field obliquity	Physicist Radiotherapist
	Preparation for treatment	Mark skin of patient	Make individual cast and/or setting up jigs Make compensating *filter* Check radiographically	Mould room technician Radiotherapist
III	*Treatment*	Check all apparatus settings Check setting up of *patient*	Independent check by second person	Radiotherapy technician (radiographer) Radiotherapist
		Immobilize patient Observe patient	Monitor beam direction (e g fluoroscopy) Monitor patient movement (e g photocell) In vivo measurement of dose during treatment	Physicist
IV	*Reconsideration*	None	Change treatment plan according to (i) results of in vivo measurements (ii) changes in patient s topography	Physicist Radiotherapist

session and supervises the irradiation In other centres the treatment, after the first session, is carried out almost entirely by trained radiotherapy technicians (or therapy radiographers *as they are called in the U K*) with only occasional supervision or intervention by the doctor Elsewhere a system somewhere between these extremes is practised Much depends on the quality and degree of training of the girls who operate the machines and the trust which the radiotherapist is prepared to place in them

Whether the treatment is carried out by the doctor or by a technician, certain rules have to be observed Errors in dosage are easily introduced by faulty settings of the controls of the machine (including inserting a wedge filter the wrong way round) by faulty setting up procedures by the use of inaccurate or badly adjusted beam directing devices and by movement of the patient during treatment All these points need attention Every stage in the procedure needs to be checked preferably by a second person Beam directing devices in particular require periodic checking since with constant use they can easily become loose or distorted It is most important to train the junior staff to look out for faults or mal adjustments in the auxiliary equipment and to report these faults immediately

In addition to the well established methods of setting up and beam directing such as the back pointer, a number of devices have recently been described which help in setting up and immobilizing of the patient (KAHR 1963 PFALZNER 1963 PEREZ TAMAYO & SEIBERT 1963) ROSWIT et coll (1960) described a simple photocell system for monitoring and restricting patient movement during treatment Further accessories designed particularly to shape the beam and protect sensitive organs were described by PROIMOS (1960 1961, 1963)

Continuous *monitoring of the beam direction in rotation therapy* by means of fluoroscopy and closed circuit television, has been tried in Sweden but the author is not aware of any publication on this subject

Finally it is possible to make direct measurements of dose during the treatment Until quite recently such measurements would almost certainly be made with small Sievert type condenser ionization chambers but nowadays a number of alternative detectors are available several of which have distinct advantages over ionization chambers However Sievert chambers will be discussed first if only because they have historical priority

The routine use of condenser chambers during treatment is highly developed in Swedish radiotherapy centres but elsewhere has been rather neglected The precautions needed to ensure the accurate functioning of these chambers have been described in detail by SKOLDBORN (1959) Measurements on the skin at the port of entry are essentially a check on the exposure calculations and on the settings of the equipment controls but give little *information as to*

Stage II is the planning stage, in which we decide on paper what we want to do. Treatment planning may be considered in four parts. First of all the radiotherapist prescribes the dose required. The prescription may comprise simply the dose in the middle of the tumour, or perhaps the minimum tumour dose, together with a maximum figure for the dose to skin or other normal tissue. Recently, however, some thought has been given to a more precise definition of 'tumour dose' (ELLIS & OLIVER 1961, SHIERS & MEREDITH 1962) and the future radiotherapist may prescribe the median tumour dose, the average tumour dose, or even the modal tumour dose, together with permitted plus and minus deviations from this value. What is really required is for the radiotherapist to describe in some detail the dose distribution he requires, or at least the distribution which he is prepared to accept.

Treatment planning now passes to the physicist and his assistants, working of course in close collaboration with the radiotherapist. The minimum requirement is the dose at a few points in the patient, assuming the patient is equivalent to a large tank of water with flat sides. The optimum solution comprises a series of alternative treatment plans, each one fully worked out for the actual dimensions of the patient and corrected for the heterogeneous structure of the body and for oblique incidence of the radiation beams. The detailed procedures which lead to a full or partial solution of this problem are too complex to show in Table I, but we shall return to this question by means of a separate table.

The last part of the planning stage is the preparation for actual treatment. This may be simply a question of putting a few ink marks on the patient's skin; on the other hand a good deal of work may be undertaken for each patient, including the production of a cast or jacket of plaster of Paris or of plastic. For therapy with roentgen rays in the conventional deep therapy range, blocks of wax are usually mounted on the cast and these serve as entrance ports for the cones or applicators defining the beams. When high energy radiation is used, however, windows are usually cut in the cast at the entrance positions of the beams and it may then be necessary to use removable jigs as aids to setting up the fields (COHEN, BURNS & SEAR 1960b). At this stage, also, a compensating filter may be constructed to compensate for the obliquity of the beams.

Stage III in clinical dosimetry is the irradiation itself. We are concerned here only with those aspects of the treatment which may affect the value of the dose delivered to the tumour and to other tissues. It is difficult to generalize because the organization of the treatment, and the personnel involved, differ widely from country to country and from institution to institution. In some clinics the radiotherapist personally sets up the patient at each treatment

session and supervises the irradiation In other centres the treatment, after the first session, is carried out almost entirely by trained radiotherapy technicians (or therapy radiographers, as they are called in the U K) with only occasional supervision or intervention by the doctor Elsewhere a system somewhere between these extremes is practised Much depends on the quality and degree of training of the girls who operate the machines and the trust which the radiotherapist is prepared to place in them

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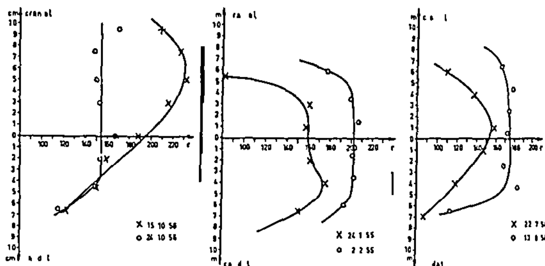


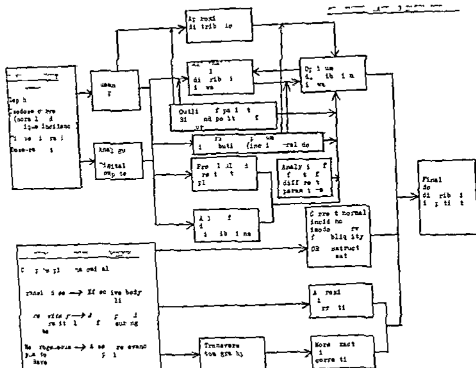
Fig 1 Doses measured in the oesophagus before and after the introduction of a compensating filter (From DAHL and VIKTERLOF 1960 by courtesy of the authors and the editor of Acta Radiologica)

the dose within the patient's body If the chambers are placed in the oesophagus, on the other hand, a direct reading is obtained of the dose within the body Great care, is needed, however, in interpreting such measurements in terms of tumour dose Apart from the physical characteristics of the chambers (e g leakage, directional properties, wavelength dependence, temperature dependence) which SKOLDBORN has shown can be closely controlled, the position of each chamber must be accurately known Furthermore, if the tumour is in the bronchus rather than the oespohagus, the difficult task remains of converting an observed discrepancy (i e measured versus calculated dose) in one position into a correction at some point or points which may be several centimetres away This problem occurs with any method of correcting for body composition and we shall return to it later in this review

In spite of these difficulties, DAHL & VIKTERLOF (1960) have demonstrated the value of intracavitary measurements A typical set of mesurements with 8 chambers in the oesophagus is shown in Fig 1 The considerable variation along the length of the oesophagus is due to the variation in the thickness of the chest in the longitudinal direction, and a compensating filter may be constructed to equalize the dose, as the later measurements show

ROSWIT and MALSKY and co workers (MALSKY et coll 1960, 1961, ROSWIT et coll 1961a, 1961b) have developed microdosimeters comprising tiny gold shielded glass rods which may be introduced not only into natural cavities of the body but even into ordinary tissues They have positioned these rods in

Table 2



the heart brain naso pharynx, floor of mouth and in several other sites As in the case of Sievert chambers in the oesophagus the difficult problem *is not the measurement but its interpretation* including the assessment of the precise position of the detector Recently ROSWIT et coll (1963) and his colleagues have initiated a general survey of in vivo dosimetry systems, while FOWLER (1963) has reviewed the whole field of solid state dosimetry including possible applications in clinical dosimetry

Perhaps the most promising phenomenon of all from the clinical dosimetry point of view is thermoluminescence Dosimeters utilizing thermoluminescent phosphors have recently been described by a number of authors including SCHULMAN et coll (1960) CAMERON et coll (1964) and KARZMARK WHITE & FOWLER (1964) The latter paper contains an excellent bibliography on the subject For in vivo measurements the phosphor of choice is lithium fluoride used in powder form in small plastic capsules Such dosimeters have many desirable properties including small size comparatively small energy depend ence linear response over a wide energy range independence from environ

mental conditions such as temperature and humidity, and small fading effect Most of the papers on thermoluminescence dosimetry have so far been concerned with the basic properties of the phosphors and read out systems, but lithium fluoride dosimeters are now being used in clinical dosimetry in several hospitals and many reports on this type of measurement may be expected in the future (e g FOWLER et coll 1965, CROSBY, SHALEK & BOONE 1965)

The results of in vivo measurements may be used to re assess the treatment and, since teletherapy is usually given in a number of sessions spread over several weeks, modifications may be made before the completion of the treatment This may be termed stage IV of clinical dosimetry It may also be necessary to modify the treatment because of changes in the patient s topography There are, of course, other methods, besides in vivo measurement, of assessing the dose for individual patients, such as the measurement of transit dose, and these will be discussed below However, these alternative techniques may be carried out before the first treatment session and the appropriate modification made right from the beginning These correction techniques have therefore been placed under stage II ('Planning') rather than stage IV But in practice this is a matter of individual preference and organization within the radiotherapy department there is no reason why transit dose or similar measurements should not be postponed until after the treatment has begun, and the application of the results of such measurements would then be 'Reconsideration' rather than 'Planning'

Treatment planning in teletherapy

Table 2 is an attempt to show the organization of the physics of treatment planning, i e stages II (A) and II(C) plus stage IV in block form This is, of course, an idealized scheme which includes all possibilities, and the path *following in an actual radiotherapy department will be a simplified version* of this diagram Basically the problem is to combine three types of data, so as to produce the final dose distribution in the patient Final in this context means two things the distribution has been deliberately chosen as being optimal for the patient concerned, and furthermore, the distribution refers to the actual, individual patient and not simply to a tank of water which may, or may not, simulate the patient The three items of data are, firstly, the physical data such as isodose curves in a homogeneous medium, secondly, the basic data referring to the patient, i e the body outline and the position of the tumour, and finally, more sophisticated data concerning the patient s anatomy from which individual corrections can be made

Until quite recently the computer used to process the data would be,

without question, a human being Some of the problems of organizing a human computer service were discussed by LINDSAY (1952) In 1955 however, TSIEN described the use of a digital computer in multiple field treatment planning (TSIEN 1955, 1958) The original method, based on polar co ordinates was suitable only for beams converging at a single point and required a considerable amount of preparatory work to convert the input data into digital form (The most recent trend is towards the use of input data in the form of field equations which may be modified mathematically to take account of variations in the geometry or discontinuities in the absorbing medium However the general argument is the same whether the input is based on experimental or theoretical data) The method was copied and further developed by STERLING et coll (1961 1963a) but in their later papers (1963b, 1964) these authors switched to a cartesian co ordinate system which is a little less accurate (since an interpolation formula has to be used) but is more versatile and entails much less preparatory work Furthermore, direct print out of the results in the correct spatial arrangement is possible A very similar system was developed independently by HALLDEN, RAGNHULT & ROOS (1963) and in its latest form this method requires less than 5 minutes to produce a complete multiple field isodose chart (See also BENTLEY 1964 HOPE & WALTERS 1964, HOPE & ORR 1965 RICHTER & SCHIRRMEISTER 1964 SCHOKNECHT 1964 WOOD 1962)

For multiple field treatment planning the major advantage of the automatic computer is its ability to reduce, almost to zero the waiting time between planning and realizing a dose distribution Thus it becomes possible to produce for each patient a number of alternative plans from which the most suitable one can be chosen In practice, however it may be difficult to convert this theoretical advantage into a workable system for routine radiotherapy In the first place only a very fast computer coupled to a good output display system (preferably an x y plotter) is able to cope with every patient in a busy radiotherapy department even assuming that only two or three alternative plans need to be calculated for each case Secondly, even if a hospital has access to such a computing system it may well prove uneconomical to utilize the computer in this way Alternative methods of programming the computer may therefore be required so as to reach the goal i e a single treatment plan optimized for the individual patient in the most efficient way For example the criteria for a good dose distribution can be decided in advance and the computer instructed to scan various combinations of parameters until these criteria are satisfied to the best possible extent Only then is a full dose distribution computed This is the approach of HOPE and ORR (1965) (The author is grateful to Mr C S Hope for allowing him to see a pre print of this paper)

If the only computer available is a human one it is virtually impossible to

base treatment planning on the computation and comparison of several complete isodose charts for every patient An alternative method, which has long been used in conventional roentgen therapy, is to calculate the dose at a limited number of discrete points, perhaps 10 or 12 but usually less, and to make the final choice on the basis of these points Recently the author has developed a new system whereby a rapid evaluation of treatment plans can be made without preparing full isodose charts, and this method will be described in part II of this paper Once the optimum arrangement has been chosen from a number of approximate distributions, the full isodose chart can be determined for this arrangement only that is why, in Table 2, a 2 way arrow links the boxes labelled 'alternative complete distributions in water' and 'optimum distribution in water' This is essentially the same approach as in the computing system, already discussed, which selects the optimum parameters before calculating a full dose distribution

The method so far, using either a human or an electronic computer, is to 'fit the treatment plan to the patient However, the opposite approach is also possible in effect, we can 'fit the patient to the plan This can be done in two ways Firstly, a set of treatment plans can be pre calculated The essential feature of a pre calculated plan is that the dose distribution is either completely independent of the contours of individual patients or, at worst, dependent on one or two variables only, which are readily assessed for each patient Secondly, treatment plans can be calculated and collected together to form an atlas An atlas differs from a random collection in so far as the charts in an atlas are classified in an agreed way and arranged according to the system adopted An atlas also differs from a set of precalculated charts in that the distributions included in the atlas are not necessarily independent of the body contour

In order to make the best use of either an atlas or a set of pre calculated plans it is highly desirable to have supplementary data available in the form of graphs or tables showing the effect of each parameter on the dose distribution Indeed, it may well be that the most useful function of the digital computer in treatment planning is to carry out such analyses The use of pre calculated charts and atlases will be considered in more detail in part II of this review We should, however, notice at this stage that whatever system of treatment planning is used, the characteristics of the individual patient and his tumour must be taken into account in selecting the optimum distribution The system determines only the point at which this information is introduced (see Table 2)

In the case of moving beam therapy, it is a fairly easy matter to compute the dose at the centre of rotation especially if the concept of 'tissue air ratio is used (JOHNS et coll 1953, 1956) but the calculation of a complete dose distribu

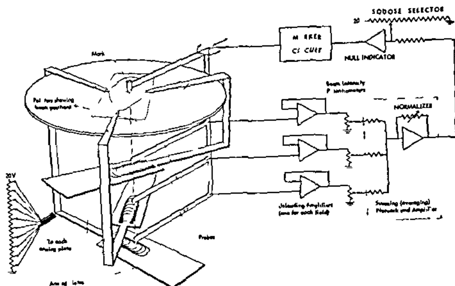


Fig 2 Diagram of analogue multiple field isodose computer showing positions of analogue plates and of the probes (From HOWARTH and PICK 1960 by courtesy of the authors and the editors of the British Journal of Radiology)

tion is very complicated and time consuming In this connection reference may be made particularly to the work of KLIGERMAN ROSEN & QUIMBY (1954), CASTRO SOIFER & QUIMBY (1955) BRAESTRUP & MOONEY (1955), JONES, GREGORY & BIRCHALL (1956) GREGORY (1957) and VAN DE GEIJN (1963b) In general these methods involve the summation of doses derived from a large number of stationary fields spaced at equal intervals of say 20 Obviously such methods are well suited to calculation by a computer and the computer techniques already mentioned in connection with multiple field additions have all been used also for moving beam therapy Indeed in the absence of a computer the quickest method of determining a complete isodose chart in rotation therapy is direct measurement in a phantom (DAHL, THORAEUS and VIKTERLOF 1956 DAHL and VIKTERLOF 1960 FOWLER and FARMER 1957 MORRISON, BEAN and KEWLEY 1957 WITCOFSKI and MESCHAN 1961) For a full bibliography of calculation and measurement methods in rotation therapy reference may be made to TSIEN CUNNINGHAM & WRIGHT (1966)

Before leaving the question of computers it is worth pointing out that the digital machine is not the only type which is able to calculate dose distributions for multiple and moving beams It is also possible to use an analogue computer in which the dose at each point of each field is represented by some physical

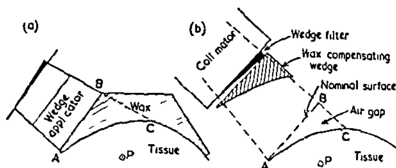


Fig 3 Method of setting up an oblique (wedge) field with deep roentgen rays using a wax jig (a) with cobalt gamma rays using a compensating filter (b) (From COHEN, BURNS and SEAR 1960b)

quantity such as electrical potential It is then a matter of placing the analogue plates, representing the various fields, in the correct spatial arrangement and adding the potentials at each point The best example of this type of computer is the machine of HOWARTH & PICK (1961) which is shown diagrammatically in Fig 2 The analogue plates are insulating plates on which conducting lines representing isodose curves are deposited These lines are connected to a low voltage source via a potential divider The space between the lines is rendered conducting by a spraying with graphite An improved method of preparing the analogue plates has been described by SKAGGS & SAVIC (1963)

Although analogue dosimetry by means of photographic films has been tried in connection with multiple radium sources (LOEVINGER & SPIRA 1957), *so far this method has not met with any success for field addition in teletherapy*

The advantage of the analogue computer, as compared with the digital machine is its much lower price Against this, however, it is only fair to point out that the analogue machine takes longer to produce a dose distribution (at least in relation to the most recent digital methods) and the digital machine, once acquired, can be used for many purposes besides treatment planning

Individual correction procedures

Up to this point we have assumed that the patient is equivalent to a tank of water The only properties of the individual which have been taken into account are his external outline and the position of the tumour We shall now consider briefly the correction procedures which may be applied to allow for the actual size, shape and composition of the individual patient In Table 2, the information derived by these procedures is used to modify the optimum water phantom treatment plan so as to produce the final distribution in the patient Strictly speaking, these corrections should be fed into the system earlier,

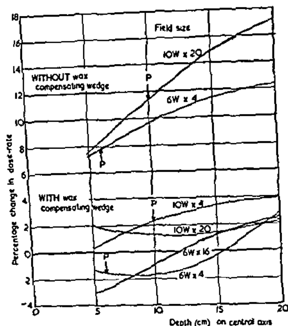


Fig 4 Dose at various depths on the central axis with and without a compensating filter (relative to dose expected from normal incidence isodose curves) (From COHEN BURNS and SEAR 1960b)

since a distribution which is optimum in a water phantom is not necessarily optimum in a real patient This however, is probably a counsel of perfection since none of these correction procedures has yet reached the stage when it can be applied easily and rapidly to alternative plans

The most important corrections are for field obliquity and for lung tissue With high energy radiation it is desirable to preserve the build up effect beneath the skin so closed applicators, wax seatings and bolus filling are not normally used (It should be noted however that this is a guiding principle not a golden rule The penetrating power of high energy roentgen and gamma rays is so high compared with that of *roentgen rays in the conventional range* that the skin dose in multiple field or moving beam irradiations is usually low even in the absence of build up If therefore it is convenient or desirable on any grounds to use bolus or wax one should not hesitate to do so — The author is grateful to Mr J B MASSEY of the Christie Hospital, Manchester, for a useful discussion on this point) One must either correct for an oblique field or use a compensator One possibility is to measure (or calculate) single

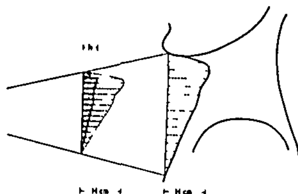
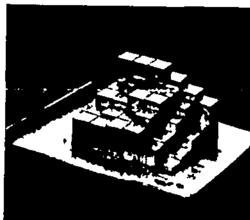



Fig 3 Metal compensating filter with allowance for beam divergence (From ELLIS HALL and OLIVER 1959 by courtesy of the authors and the editors of the British Journal of Radiology)

field isodose curves in a water phantom at a series of angles of incidence (CAMPBELL & THAN TUN 1964) The application of this method assumes, however, that the surface of the patient is reasonably flat Frequently, however, the body surface is markedly curved and it is then desirable to correct the original isodose curves (measured either at normal incidence or at the nearest oblique angle) so as to take account of the actual contour of the patient ICRU Report No 10d (1963) describes three acceptable methods of making this correction the effective SSD method, which corrects essentially by inverse square law along each ray, the effective attenuation coefficient method (MURISON & HUGHES 1957), in which the effective absorption along each ray is taken into account, e g 4 5 % per centimetre for cobalt gamma rays, finally, the isodose shift method (DUTREIX & DUTREIX 1962, GARRETT & JONES 1962, FARR 1963) which is an empirical method but nevertheless satisfactory Recently a new method, based on tissue air ratios, has been described by DU SAULT & LEGARE (1963)

The alternative to correction is compensation, i e to replace the 'missing' tissue by a similar wedge shaped block of material which is placed sufficiently far back in the beam to avoid irradiating the surface with secondary electrons which would destroy the build up effect (Fig 3) Obviously the absorption of radiation in a given mass of absorber is the same whatever its position in the beam, and only the contribution of scattered radiation from the 'missing tissue to points deeper in the body is lacking Fortunately, for high energy radiation this scatter contribution is relatively small and can be allowed for by making the thickness or density of the compensating filter a few per cent less than would otherwise be needed The accuracy of the method is illustrated in Fig 4

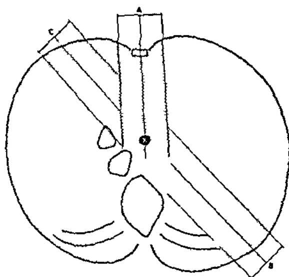


Fig 6 Arrangement of beams so as to avoid irregularly shaped lung tissue (From STEWART 1962 by courtesy of the author and the editors of the British Journal of Radiology)

If the source skin distance is large so that the beam divergence is small the easiest way to construct a compensating filter is to mould a block of wax of density 0 95 g/cc directly on the skin of the patient (COHEN, BURNS & SEAR 1960b) Usually however it is necessary to take account of beam divergence and a metal compensator is constructed as described by ELLIS HALL & OLIVER (1959) (Fig 5) (See also HALL & OLIVER 1961 VAN DE GEIJN 1963b)

Correction for body composition

The heterogeneous nature of the human body gives rise to many problems in clinical dosimetry and we cannot hope to deal with this subject adequately in a short review Only a few important features of the problem will be discussed here with particular reference to the practical correction procedures

When roentgen rays of low and medium energy are used for therapy the dose distribution pattern measured in water is seriously distorted by both bone and lung tissue (SPIERS 1946) It is indeed now widely appreciated that *conventional* roentgen rays should be avoided for therapy in body regions in which an appreciable mass of bone occurs If we confine our attention to high energy radiation however (including cobalt gamma rays) only lung presents any serious problem The low density of lung tissue (0 25 to 0 4 g/cc) reduces both the attenuation of radiation and the production of scattered radiation In general the attenuation effect is more important so that the dose in a lung or oesophageal tumour is higher than would be expected from water phantom

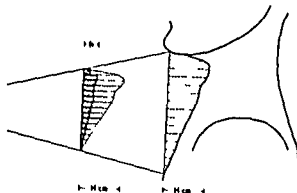
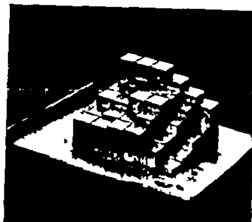



Fig 3 Metal compensating filter with allowance for beam divergence (From ELLIS HALL and OLIVER 1959 *by courtesy of the authors and the editors of the* British Journal of Radiology)

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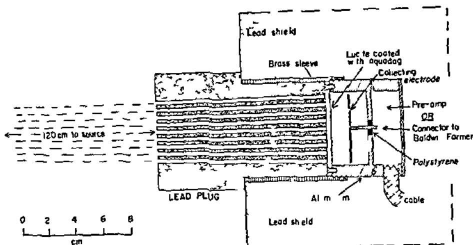


Fig 8 Focussed transit chambe (From FEDORUK and JOHNS 1957 by courtesy of the authors and the editors of the British Journal of Radiology)

A somewhat different and more individualized approach to body heterogeneity is to measure the dose transmitted through the patient and hence assess the difference between the actual absorption and that expected in a unit density medium If the measurements are made with the same broad beam of radiation as is used for the treatment the effect of scattered radiation must be avoided and so a small transit chamber must be *enclosed in* a shield as shown in Fig 7 (O CONNOR 1956) or alternatively a large flat chamber is placed behind a collimating device (Fig 8) which accepts only the primary radiation (FEDORUK & JOHNS 1957) This instrument was designed to be housed in the counterweight of a cobalt rotating unit A transmission chamber which accepts the whole of a broad beam of radiation, even if the scatter component is excluded gives the average transmission over the whole cross section of the beam More detailed information *for individual rays is obtained by means* of measurements with a collimated scintillation counter used in conjunction with a weak cobalt source This method is being developed by HOLODNY et coll (1964) and enables an effective contour to be plotted as shown in Fig 9 A transmission chamber divided *into 7 sections has recently been described by* NORDBERG (1963)

Instead of a transmission chamber it is also possible to use an exit chamber i e one which is placed on the exit surface of the patient (WOODLEY BRONSTEIN & LAUGHLIN 1960) but in this case the relationship between the exit dose and the transit dose must first be found by careful calibration

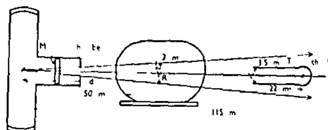


Fig 7 Shielded transit chamber (From O CONNOR 1956 by courtesy of the author and the editors of the British Journal of Radiology)

measurements The increase may be 20 per cent, or even more, depending on the energy of the radiation and the precise geometrical relationship between the tumour and the lung tissue traversed by the radiation beam For a given tumour, the correction depends on the path and direction of each beam, and one way of simplifying the correction problem is to avoid directing beams in such a way that the tissue traversed includes a triangular or irregularly shaped block of lung This point is illustrated in Fig 6, which is taken from STEWART (1962)

The simplest approach to the lung problem is to apply a correction factor which depends only on the radiation energy (JACOBSON & KNAUER 1956 a and b, MASSEY 1962) For example, when a beam of cobalt gamma rays traverses 5 to 8 cm of lung tissue, the dose at subsequent points is increased by 20 % Somewhat more complex corrections, which take into account the position of the tumour in relation to the lung tissue, were proposed by DUTREIX, DUTREIX & TUBIANA (1959, 1960)

Recently GREENE & STEWART (1965) have made a series of measurements in a water phantom in which air cavities, bone and 'lung' specimens could be inserted As a result, these authors have suggested a few simple correction rules for shifting the isodose lines following a discontinuity For example, for cobalt 60 or 4 MV radiation the lung correction proposed is simply a distal shift of the isodose lines following the lung by 0 4 times the thickness of the lung along rays parallel to the central axis of the beam Similar correction factors are for air cavities 0 6, for hard bone 0 5, and for spongy bone 0 25 (Bone requires a greater correction than lung per unit thickness, but the volume of bone involved is usually small) Corresponding corrections are given for conventional roentgen rays (2 5 mm Cu HVL) GREENE & STEWART show further that, while the absolute dose rate due to single radiation beams is modified by the presence of lung, etc, as just indicated, the relative dose distribution in the central region of a multiple field isodose chart is changed very little It may also be noted that the measurements of these authors did not embrace the important case of a tumour situated within lung tissue

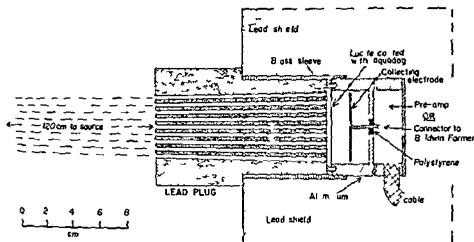


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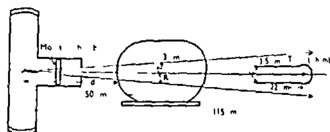
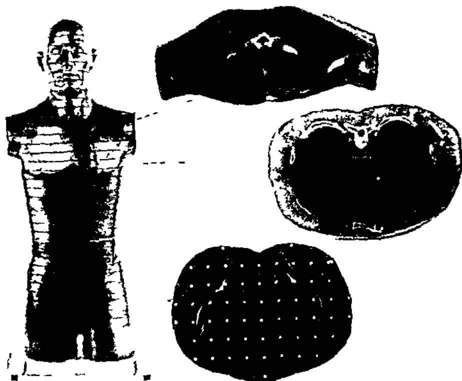


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Fg 11 Alderson Bando phantom system showing the Average man Rando phantom and typical phant m cr ss sections (F om Alderson Research Labs Techn cal Bulletin No 3ɔ by courtesy of Alderson Resea ch Labs Inc

assume that the whole path of the beam absorbs uniformly but to a less extent than water This gives curve B, which is a better correction than none at all In reality however the curve is discontinuous depending on the thicknesses traversed of soft tissue lung and again soft tissue This is shown in curve C (For simplicity the further discontinuities due to the ribs are omitted) If the lung section is not symmetrically placed the curve will depend on the direction in which the beam travels Obviously some knowledge of the cross sectional anatomy of the patient is needed if the results of transit or similar measurements are to be correctly interpreted Even an approximate estimate based on anatomical atlases is better than nothing, but for a comprehensive and accurate cross section of an individual patient it is necessary to use transverse tomography

The methods we have discussed so far can be used on a routine basis, for correcting the tumour dose when the thorax is irradiated but a good deal of

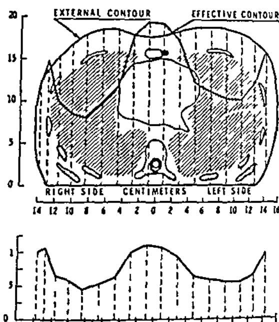


Fig 9 Effective body outline as measured by scintillation counter (From HOLODNY et coll 1964 by *courtesy of the authors* and the editors of Radiology)

The measurement of either an exit or a transit dose does not in itself, however, provide sufficient information for correcting the tumour dose The effective thickness merely tells us that the absorption curve in water (curve A in Fig 10) is not applicable In the absence of any other information we can only

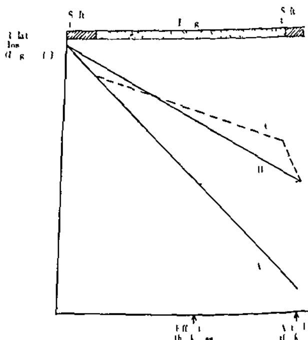


Fig 10 Depth dose curves in the thorax
Curve A assuming unit density throughout
Curve B assuming less than unit density throughout as indicated by transit dose measurement
Curve C with knowledge of thickness of lung traversed (neglecting effect of ribs)

D Differences in dimensions of irradiated region and the phantom in which the doses were measured

E Composition of the body

2 *Setting up for treatment*

A Marking of skin

B Fitting of jacket plaster cast etc

C Adjustment and use of beam directing and other auxiliary devices

D Insertion of wedge filter

E Adjustment of treatment position of the patient

F Setting of SSD

G Type and arrangement of bolus

3 *Exposure*

A Output variations

B Calculation errors

C Human errors in setting the meters on the radiation machine and delivering the exposure

There is no golden path which leads to the elimination of errors in clinical dosimetry However certain rules have been found helpful

1 Use high energy radiation

2 Organize the clinical dosimetry service and the actual delivery of the radiation so that the various procedures are always carried out in the same sequence and each step is checked before the next is begun

3 Train all staff particularly junior and auxiliary personnel, to understand the meaning and purpose of each procedure since errors are more likely if operations are carried out in parrot fashion

4 Check the accuracy and alignment of auxiliary equipment (e g beam directing devices) at regular intervals

SUMMARY

A review is presented of the procedures whereby an irradiation treatment is planned and delivered to an individual patient and the value of the tumour dose assessed Four stages may be distinguished in clinical dosimetry topography planning treatment and reconsideration These stages are discussed in relation to teletherapy with the aid of tables and a block diagram Emphasis is laid on individual correction procedures for body shape and composition by calculation by in vivo measurement or by measurement of transit doses The possible role of automatic computers in clinical dosimetry is also discussed

additional work is involved if the complete distribution throughout the body section, and not simply the dose at one or two points, is to be corrected. Although this problem is theoretically soluble it is doubtful if the effort required is justified unless a computer is available. A promising alternative approach is to use a tissue compensating filter as proposed by HALL & OLIVER (1962), and by ELLIS, FELDMAN & OLIVER (1964).

An alternative method of determining the dose distribution throughout the body section is to measure the distribution in an anatomical phantom, i.e. a phantom designed to resemble an average human being in size and structure (e.g. COHEN 1955, DAHL & VIKTERLOF 1960). Recently a complete phantom system, which is intended for routine computation of treatment plans on an analogue basis, has been devised by ALDERSON et coll. (1962) and is available commercially (Alderson Rando System, 1961) (Fig. 11). The main difficulty in such a system is to translate the phantom measurements into a dose distribution in an individual patient. An attempt is being made to simplify this transfer by constructing a number of phantoms of different sizes so that the measurements can be made in a phantom of approximately the correct size.

Summary of sources of error (based on Section IX of ICRU Report 10d)

To conclude the discussion on clinical dosimetry in teletherapy, which began with Tables 1 and 2, the possible sources of error are summarized below. A more extensive list, including the errors involved in calibration of dosemeters, measurement of output and of isodose curves and similar topics excluded from this review, has been given in the report cited above. We must resist the temptation to add numerical values to each error, as the extent of the error likely, or even possible, depends on the individual circumstances. MARTIN, EVANS & ANDERSON (1960), in a somewhat similar table of errors, included estimates of magnitudes, but many of these estimates were apparently based on roentgen sets used for rather superficial irradiation. Such estimates can be quite misleading if applied to high energy machines.

1. *The patient*
   - A. Estimation of contour
   - B. Localization of tumour
   - C. Changes in (A) and (B)
     - during the course of treatment
     - according to position of the patient
     - through movement of patient during exposure

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HIGH ENERGY ELECTRON THERAPY AND THE TWO COMPONENT THEORY OF RADIATION

by

R WIDEROE

In recent years investigations on irradiated cell cultures have cast new light on radiobiologic effects and also aroused widespread hopes that with these findings radiotherapy could be better understood and problems solved, resulting in better methods for the treatment of tumors

To-day we know that most of the investigated normal and cancerous mammalian cell cultures show approximately the same radiosensitivity (ELKIND 1960) We know also that roentgen irradiated surviving cells in a culture will recover completely (Elkind recovery ELKIND et coll 1964) in a relatively short time after the irradiation (about 10 hours or less) We have further established survival curves (dose effect relations) for various kinds of radiation and also studied the influence of the surroundings (oxygen pressure, injection of cysteamine etc) on the radiosensitivity of the cells in vitro (BARENDSEN 1964)

On the occasion of a Symposium on Fractionation and Dose Rate Westminster London in 1962 many attempts were reported trying to link the medical experiences in radiation therapy with the radiobiologic results and several new treatment schemes were suggested *Similar ideas have in the*

From the Swiss Federal Institute of Technology Zurich Switzerland. Submitted for publication 26 July 1965

ZUSAMMENFASSUNG

Es wird eine Übersicht uber die Massnahmen zur Planung und Durchfuhrung einer individuellen Strahlenbehandlung sowie uber den Nutzen der erhaltenen Tumordosis gegeben In der klinischen Dosimetrie konnen vier Stufen unterschieden werden Topographie Planung Behandlung und erneute Überprufung Diese Stadien werden mit Hinsicht auf Teletherapie an Hand von Tabellen und einem Blockdiagramm diskutiert Besonderer Nachdruck wird gelegt auf individuelle Korrektur mit Rucksicht auf Korperform und Zusammensetzung mittels Berechnung in vivo Messungen oder Messungen der durchdringenden Dosis Es wird ebenfalls besprochen inwieweit die Anwendung von automatischen Rechenmaschinen in der klinischen Dosimetrie moglich ist

RÉSUMÉ

L auteur rapelle les techniques qui servent dans chaque cas particulier à établir le plan d un traitement par les radiations et à l appliquer et à calculer la dose à la tumeur On peut distinguer quatre phases en dosimétrie clinique étude topographique établissement du plan de traitement, traitement étude ultérieure Des tableaux et un diagramme facilitent l étude de ces phases pour la téléthérapie L auteur insiste sur les techniques de correction tenant compte de la forme et de la composition du corps utilisant le calcul les mesures in vivo ou la mesure des doses de transit Il examine aussi le role possible des calculatrices automatiques en dosimétrie clinique

REFERENCES

To be given in part II of this paper

Fig 2 A comparison of some results of radiation treatment of bronchial carcinoma The conventional roentgen treatments show 1 year results with 20 to 30 survivals (3 year results give less than 10 survivals) whereas treatments with Co rays give somewhat better 1 year results So far the results with high energy electrons using high single doses appear to be superior

results than the commonly used daily doses of 200 to 300 rad with conventional roentgen or megavolt irradiation The early treatment results are as good as for the operated patients (even when inoperable cases were treated) with one year survival of about 50 % as for patients of stages II and III SCHUMACHER s results and a comparison with other results of radiation treatments, are shown in Figs 1 and 2 (In the meantime the results with a high single dose treatment have been verified in other hospitals)

Favourable results with high energy electrons using conventional treatment doses have been reported by several hospitals (VERAGUTH 1961) with different cases The good results may partly be due to a suitable dose distribution and a small integral dose (WIDEROE 1959 1961) but also specific biologic effects seem to make treatment with electrons more tolerable for the patients and lead to a favourable recovery of irradiated tissue This makes it possible to administer much higher single doses with electrons than with other types of radiation

For over 4 years now in the Rudolf Virchow Hospital in Berlin (SCHUMACHER) single tumor doses of 500 to 600 rad given twice a week or 1 000 to 1 200 rad given once a week have been used (With single doses of 1 000 to 1 200 rad the first interval between irradiations is one week the next interval

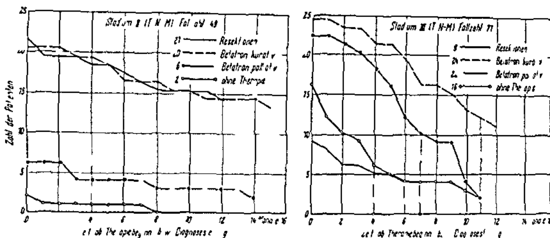


Fig 1 Survival index for 120 patients with effectively proved bronchial carcinoma stages II and III depending on therapy (SCHUMACHER 1964)

meantime been discussed also by other investigators (e g ANDREWS 1965, HUG 1964) (It is impossible here to describe in detail all attempts but the reader may get a good impression of the situation by studying the cited literature, especially Brit J Radiol 36 (1962) pp 153—196)

To day, developments in radiation therapy are progressing rapidly The use of megavolt roentgen rays and especially deep therapy with high energy electrons has increased our understanding and improved results However, not all the experiences can be physically explained by the better dose distribution and the reduced integral doses (GAUWERKY 1964)

In the present paper, a case treated with high energy electrons will be described and it will be shown that results from cell cultures are not directly applicable to such conditions (WIDEROE 1965) The reason is discussed and a new quantitative theory for radiation effects in vivo is advanced

Treatment example from radiation therapy

We will discuss the treatment of bronchial carcinoma using 35 MeV electrons Early bronchial carcinoma has already been treated with high energy electrons but the results were mostly discouraging and not much better than those obtained by conventional radiation therapy (ZUPPINGER et coll 1964) Only UHLMANN & OVADIA (1961) and HELLRIEGEL (1959) have reported somewhat better results with lesions of early stages Recently, however, SCHUMACHER (1964) has demonstrated that higher single doses, given at greater intervals (for instance up to 1 200 rad tumor doses given once a week) give much better

Fig 2 A comparison of some results of radiation treatment of bronchial carcinoma The conventional roentgen treatments show 1 year results with 20 to 30 % survivals (3 year results give less than 10 % survivals) whereas treatments with Co rays give somewhat better 1 year results So far the results with high energy electrons using high single doses appear to be superior

results than the commonly used daily doses of 200 to 300 rad with conventional roentgen or megavolt irradiation The early treatment results are as good as for the operated patients (even when inoperable cases were treated), with one-year survival of about 50 %, as for patients of stages II and III SCHUMACHER s results and a comparison with other results of radiation treatments are shown in Figs 1 and 2 (In the meantime, the results with a high single dose treatment have been verified in other hospitals)

Favourable results with high energy electrons using conventional treatment doses have been reported by several hospitals (VERAGUTH 1961) with different cases The good results *may partly be due to a suitable dose distribution and a* small integral dose (WIDEROE 1959 1961) but also specific biologic effects seem to make treatment with electrons more tolerable for the patients and lead to a favourable recovery of irradiated tissue This makes it possible to administer much higher single doses with electrons than with other types of radiation

For over 4 years now in the Rudolf Virchow Hospital in Berlin (SCHUMACHER) single tumor doses of 500 to 600 rad given twice a week, or 1 000 to 1 200 rad given once a week, have been used (With single doses of 1 000 to 1 200 rad the first interval between irradiations is *one week the next interval*

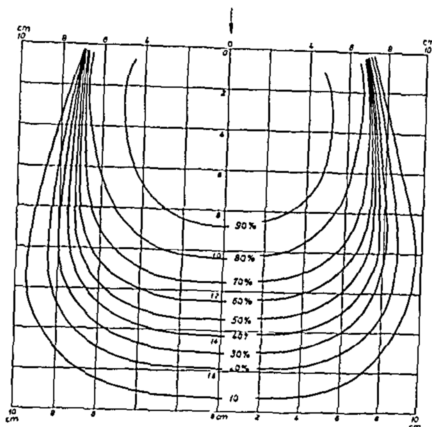


Fig 3 Isodose curves measured in water for 35 MeV electrons with a (14 × 14) cm² field and at a 1 1 m focus skin distance

two weeks and for further irradiations 4 weeks) They lead to a rapid disappearance of the tumor, after 3 weeks, radiography of the lungs has shown definite improvement The high single doses are tolerated remarkably well by the lung tissue, even in patients who are in a generally bad state (having for example abscesses, haemophtysia or lung tuberculosis) The irradiation in many cases causes radiation pneumonitis which can be successfully treated with cortisone, calcium diuretin and antibiotics (DEELY 1960) It is necessary to have patients in this stage watched carefully and treated by a lung specialist, so as to avoid any false interpretation of the radiodiagnostic findings (LOEBBROKS & SCHUMACHER)

Cell survival with high single doses will now be discussed Isodose curves for 35 MeV electrons in water are given in Fig 3, and in Fig 4 the dose distribution in a 18 cm thick body treated contralaterally with 35 MeV electrons is shown The conditions might differ somewhat when the lung is irradiated, the density of the lung with air will be less, the thickness of the body

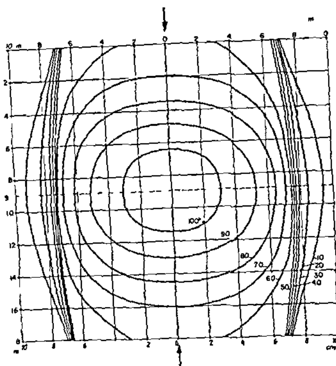


Fig 4 Isodose curves in a water phantom of 18 cm thickness irradiated with 35 MeV electrons from two contra lateral fields (14 × 14) cm FSD = 1.1 m

may be greater but the curves in Fig 4 will grosso modo be typical for most of such treatments Survival curves of heteroploid human kidney cells (T_1 cells), irradiated in cell cultures with roentgen rays and with electrons from ^{90}Y having a maximum energy of 2.18 MeV are given in Fig 5

The measurements made by BARENDSEN some years ago (1961) show the typical response of mammalian cells to irradiation In a semi logarithmic display the curves show a shoulder for small doses while they are linear for large doses If we apply the survival results of the kidney cells onto the dose distribution of Fig 4 we get iso survival curves as shown in Fig 6 On the left hand side of the diagram the central single dose is 1 200 rad on the right hand side the single dose was taken to be 300 rad From this we see that a single dose of 1 200 rad would kill more than 95 % of all cells at all depths in the body The kidney cells are not especially radiosensitive, the sensitivity of

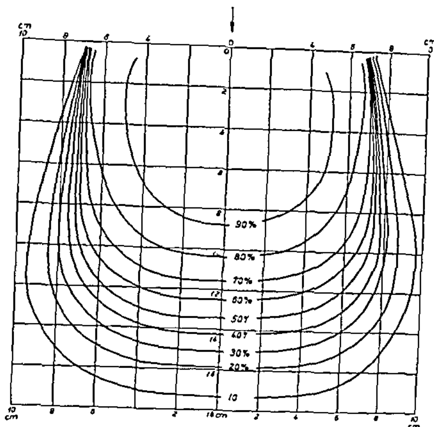


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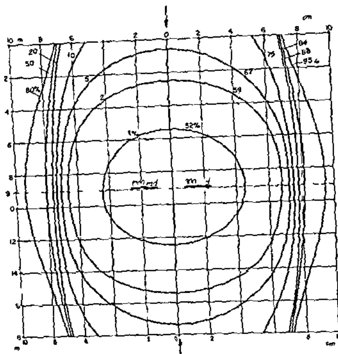


Fig. 6. Iso-survival curves showing the surviving cells in a body irradiated contra laterally with 35 MeV electrons as in fig. 4 using the survival rates (for electrons) of fig. 5. On the left hand side the single central dose is 1200 rad, on the right hand side the dose is 300 rad.

crepancy and most probably, we have to look at the various recovery effects for the damage caused to cells in vitro and in vivo.

The primary radiation cell damage caused in vivo and in vitro is probably nearly the same considering equal cytologic and ionizing conditions, but afterwards the roads divide. When a body is irradiated recovery processes start: the body reservoirs of enzymes and spare parts for production of proteins and other macromolecules are mobilized and a great deal of cell damage may be repaired, while cells in cultures without such recovery potentials die out. From this we learn that recovery processes starting immediately after the irradiation represent a very important secondary phase which in a high degree may decide the resulting radiosensitivity of the cells in vivo. This recovery should of course not be confused with the short time Elkind recovery acting in irradiated cell cultures which probably is based on the local intercellular recovery potential (ELKIND & SUTTON 1964).

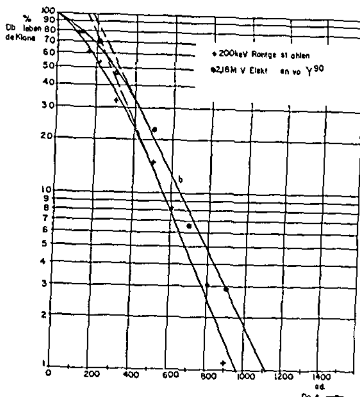


Fig. 5. Surviving reproductive human kidney cells (T_1 cells) irradiated in cell cultures with 200 keV roentgen rays (HVL = 1.9 mm Cu) and electrons from ^{90}Y (2.18 MeV max.) (BARENDSEN 1961).

the lung parenchyma should be at least equal. A single dose of 1 200 rad should therefore, roughly speaking, burn a big hole through the body and why this does not happen remains to be explained.

At the Westminster Symposium in 1962 (see ref. 'Fractionation and Dose Rate') it was proposed (by Professor Ellis, and others) that the radiation damage stimulates the normal cells to step up proliferation to a very high rate; they repopulate the irradiated tissue by cell division and thus close the hole in the interval between irradiations. — In this article we shall employ the terms 'regeneration' or 'repopulation' when the radiation damage is restored by division of the surviving cells, thus creating virtually the same tissue as before; the term 'repair' will be used when scar tissue is also produced after the radiation damage. — This explanation, however, seems quite unsatisfactory. A certain degree of repopulation may occur but a complete regeneration of such a major damage does not seem possible (see FOWLER, and STERN in 'Fractionation and Dose Rate'). We have to find other explanations for this dis

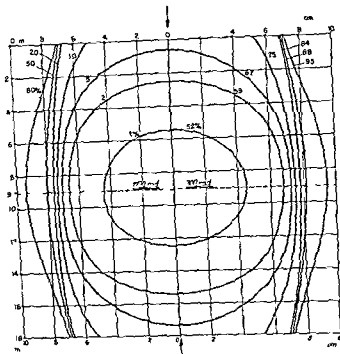


Fig 6 Iso-survival curves showing the surviving cells in a body irradiated contra laterally with 3 MeV electrons as in fig 4 using the survival rates (for electrons) of fig 5 On the left hand side the single central dose is 1 200 rad on the right hand side the dose is 300 rad

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The primary radiation cell damage caused in vivo and in vitro is probably nearly the same considering equal cytologic and ionizing conditions but afterwards the roads divide When a body is irradiated, recovery processes start the body reservoirs of enzymes and spare parts for production of proteins and other macromolecules are mobilized and a great deal of cell damage may be repaired while cells in cultures without such recovery potentials die out From this we learn that recovery processes starting immediately after the irradiation represent a very important secondary phase which in a high degree may decide the resulting radiosensitivity of the cells in vivo This recovery should of course not be confused with the short time Elkind recovery acting in irradiated cell cultures which probably is based on the local intercellular recovery potential (ELKIND & SUTTON 1964)

When investigating mammal cultures of normal and tumor cells, we essentially find nearly the same radiosensitivity (differences up to a factor of 2 or 3 have been found BARENDSEN 1964) and this is quite contrary to many cases in clinical radiotherapy where we have very great differences in radiosensitivity This contradiction also shows clearly that the conditions in cell cultures must be very different from the situation in vivo where obviously the recovery phenomena are of decisive importance (HUG 1964)

The various attempts made in England and America to draw conclusions directly from cell cultures and relate them to radiotherapy, regardless of such recovery effects, would seem to be condemned to fail

The amount and kind of radiation delivered to the cell is certainly of great importance The primary damage is the starting point for all further processes, and the magnitude, type and intensity of the radiation are crucial for the recovery effects and for the results of treatment

We will now develop a mathematical theory based on these ideas and thereby try to cover the radiobiologic as well as the therapeutic facts It is our hope that such a theory might stimulate quantitative research in radiotherapy and thus lead to a better understanding and improved methods of treatment

Radiobiologic and radiotherapeutic effects described by means of a two component theory of radiation

The ion distribution in a cell irradiated with 200 rad of 30 MeV electrons is shown in Fig 7 The ions produced during the irradiation have been printed in the form of 440 small dots on an electron microscopic image of a non irradiated lymph node cell of a mouse (courtesy of GOLDFEDER 1962) The image measures (3 73 × 4 2) μ^2 and the slice is supposed to have a thickness of 0 13 μ It will be hit by 32 high energy electrons, crossing from left to right With a commonly used dose rate of 200 rad per minute the slice of tissue which measures 0 545 μ^2 *of surface (facing the electron beam)*, will be hit by one high energy electron every 1 87 second An accumulation of the effects from various primary tracks is therefore only possible for relatively long lasting ionization effects

More than 90 % of the ions produced by the high energy electrons will be deposited as so called 'primary ions' very close to the track of the primary electron These ions are fairly equally distributed, often 2 or 3 are found together in small clusters and the average density of the ionization is very low In certain cases, however, the primary electron may also produce a secondary electron of such an energy (for instance more than 700 to 800 keV) that it creates a separate track of ions (δ ray) branching off from the track of the



Fig 7 Pa t of a lymph node cell of a mouse PM is the plasma membrane surround ng the cell ER the endoplasmic reticulum RNP r bonucleose particles M mitochondria and N the rucleus w th its double memb ane DM A portion of another cell can be seen below superimposed black dots are ions p oduced by 200 rad delivered by 30 MeV electron irradiation δ are two secondary electr ns with a joint energy of 9 6 keV (Electron micrograph courtesy of GOLDFEDER 1962)

mary ion track and such a δ-track will end up in a bigger ion cluster ntaining about 22 ions in the last $\frac{1}{3}$ μ of the track It is obvious and it has en been mentioned (WIDEROE 1960 ROSSI 1964) that such a concentrated oup of ions will cause a much more profound and massive effect in the cell an the sparsely distributed primary ions It even seems possible that a certain mber of such δ-ion clusters hitting a sensitive part of the cell might cause tal non reversible effects such as a destruction of the nucleus or the mem ane system leading to acute or delayed death of the cell With 30 MeV ectrons relatively few such big ion clusters are produced but 30 MeV roentgen ys produce some more and 200 keV roentgen rays a great many more (about to 5 times as many) which shows that not only the strength of the dose but

also the type of radiation decides if an irradiated cell shall die out, be sterilized or recover.

BARENDSEN (1964), and others, have mentioned that every radiation can be considered as made up of various components each producing a different density of ionization (LET-value). In this way, the influence of fractionation, protraction, and oxygen pressure, on the survival of irradiated cell cultures can be explained. In order to link radiobiology with radiotherapy, we will now try to extend this idea to irradiations *in vivo*.

For the sake of simplicity, we suppose that the radiation is composed of only two components, a dense ionizing 'α component' with high LET values and a scarcely ionizing 'β component'. The part of the total dose produced by the α component will be designated a. Alpha rays with an energy of a few MeV (^{210}Po produces 5.3 MeV alpha rays) consist nearly entirely of an α component ($a = 100$ %). Roentgen rays of 100 to 200 keV maximum energy probably contain an α component of about 10 to 20 %, whereas 30 MeV roentgen rays may have a-values of 5 to 7 %, and 30 MeV electrons probably only 3 to 5 %. (The a numbers are estimated so as to suit radiobiologic measurements and also preliminary calculations on the number of δ rays for various radiations.)

Investigations on irradiated cell cultures have established the dose/effect relations for the two components. The α component gives an exponential relation of the number S_α of the surviving cells for a dose D

$$S_\alpha = e^{-aD/D_{0\alpha}} \tag{1}$$

where $D_{0\alpha}$ is the dose at which $S_\alpha = 1/e = 36.8$ % of the cells survive. It does not seem possible to irradiate cells with an entirely 'clean' β component (we always get some δ electrons and consequently also a small α component), and we shall therefore have to evaluate the dose effect relation for the solitary β component from measurements with a mixed radiation, subtracting the influence of the α component. In a semilogarithmic display, we then get the well known 'shoulder curves' for the survival numbers due to the β component which can be represented by the relation

$$S_\beta = 1 - (1 - e^{-(1-a)D/D_{0\beta}})^p \tag{2}$$

where p is the extrapolation number and $D_{0\beta}$ again the 36.8 % dose value for the linear part of the curve (semilogarithmic representation). Measurements by BARENDSEN (1961) have shown that the resulting number S_Σ of surviving cells will be the product of the survivals for the various components, which also means that the killing effects of the two radiation components are independent of each other. BARENDSEN measured the survival of cells irradiated by alpha rays and shortly after with roentgen rays. This should in principle not

Table I

Cell survival (S_-) in vivo for normal cells as a function of dose (D)

$$S_\Sigma = e^{-aD/D_{0a}} \left[1 - \left(1 - e^{-(1-a)D/k\,D_\beta}\right)^p\right]$$

D_{0a} = 100 rad D_β = 200 rad extrapolation number p = 3 recovery factor k = 5 (normal cells)

a =	D =	100	200	300	500	1 000	1 200	1 500	2 000 rad
0	$S_\beta = S_\Sigma =$	99 92	99 4	98 3	93 9	74 7	66 0	53	35 9
	S =	96 95	93 8	91 4	86 0	74 1	69 7	63 8	54 9
	S_β =	99 97	99 45	98 38	94 3	76 0	67 6	55 2	37 0
3	S_- =	96 87	93 25	89 8	81 1	56 4	47 1	35 2	20.3
	$\frac{1-S_\beta}{1-S}$ =	7 6	8 9	19 0	40 7	92 7	107	124	140
	S =	95 0	90 6	86 0	77 9	60 6	54 9	47 2	36 8
	S_β =	99 92	99 49	98 48	94 51	76 7	68 6	56 5	38 0
5	S_Σ =	94 92	90 1	84 7	73 55	46 5	37 8	26 9	14 0
	$\frac{1-S_\beta}{1-S}$ =	1 6	5 4	10 8	24 7	59 2	69 6	82 4	98
	S =	90 5	81 9	74 1	60 6	36 8	30 1	22 3	13 5
	S_β =	99 93	99 55	98 68	95 25	79 1	71 0	59 2	42 0
10	S_- =	90 47	81 3	73 1	57 7	29 1	21 4	13 2	5 66
	$\frac{1-S_\beta}{1-S_a}$ =	0 7	2 5	5 1	12 0	33 0	41 5	52 5	67 0
	S =	86 0	74 1	63 7	47 15	22 3	16 55	10 53	4 98
	S_β =	99 95	99 62	98 85	95 87	81 3	73 8	62 7	45 4
15	S_- =	86 0	73 8	63 0	45 2	18 1	12 2	6 6	2 26
	$\frac{1-S_\beta}{1-S}$	0 36	1 47	3 17	7 82	24 1	31 4	41 7	57 5
	S =	81 9	67 0	54 9	36 8	13 5	9 1	4 98	1 91
	S_β =	99 96	99 68	99 02	96 4	83 4	76 5	66 0	49 1
20	S =	81 8	66 7	54 4	35 5	11 25	6 96	3 28	0 94
	$\frac{1-S_\beta}{1-S}$ =	0 25	0 97	2 04	5 7	19 2	25 8	35 8	51 9
100	$S = S_- =$	36 8	13 5	4 98	0 667	0 0046	—	—	—

be different from a simultaneous irradiation with rays composed of two components

$$S_\Sigma = S_\beta \; S \tag{3}$$

and thus for the total survival

$$S_- = e^{-a\,D_{0a}} \left[1 - \left(1 - e^{-(1-a)D}\,{}_{D_\beta}\right)^p\right] \tag{4}$$

Table 2

Cell survival (S_Σ) in vivo for tumor cells having a recovery factor $k = 2$, $D_{o\alpha} = 100$ rad $D_{o\beta} = 200$ rad $p = 3$ $1-S_\beta/1-S_\alpha$ = relation between the cells killed by the β-component and the α-component

$a =$	$D =$	100	200	300	500	1 000	1 200	1 500	2 000 rad
	$S_\alpha =$	95 0	90 6	86 0	77 9	60 6	54 9	47 2	36 8 %
	$S_\beta =$	99 06	94 6	86 8	66 5	25 0	16 0	8 0	2 5 %
5 %	S_Σ %	94 1	85 6	74 5	51 8	15 1	8 8	3 78	0 92 %
	$\frac{1-S_\beta}{1-S_\alpha} =$	18 8	57 5	94	152	190	186	174	154 %
	$S_\alpha =$	90 5	81 9	74 1	60 6	36 8	30 1	22 3	13 5 %
10 %	$S_\beta =$	99 19	95 22	88 2	69 4	28 4	18 9	10 0	3 2 %
	$S_\Sigma =$	89 8	78 0	65 3	42 05	10 45	5 69	2 23	0 43 %
	$\frac{1-S_\beta}{1-S_\alpha} =$	8 5	26 4	45 6	77 6	113	116	116	112 %
	$S_\alpha =$	86 0	74 1	63 7	47 15	22 3	16 55	10 53	4 98 %
	$S_\beta =$	99 3	95 85	89 5	71 9	39 2	21 5	12 2	4 0 %
15 %	$S_\Sigma =$	85 4	71 7	57 0	34 0	7 1	3 56	1 29	0 20 %
	$\frac{1-S_\beta}{1-S_\alpha} =$	5 0	16	29	53 2	78 3	94	98	101 %
	$S_\alpha =$	81 9	67 0	54 9	36 8	13 5	9 1	4 98	1 91 %
20 %	$S_\beta =$	99 4	96 4	90 8	74 8	35 0	25 0	14 0	5 5 %
	$S_\Sigma =$	81 3	64 6	49 8	27 5	4 72	2 28	0 7	0 105 %
	$\frac{1-S_\beta}{1-S_\alpha} =$	3 5	11 3	20 4	40 0	75 2	92 7	90 5	96 3 %

In the following discussion, we will suppose $D_{o\alpha}$ to be 100 rad (corresponding to a LET-value of about 57 keV/μ) and $D_{o\beta}$ to be 200 rad with an extrapolation number $p = 3$ With these values, we get survivals for $a = 100$ % (alpha rays from ^{210}Po) and $a = 15$ % (200 keV$_m$ roentgen rays) which correspond well to the measurements of BARENDSEN (1964)

We *now postulate, when irradiating cells in vivo, that to* satisfy the clinical experience, the dose constant D_o has to be multiplied by a recovery factor k (also the extrapolation number p might change but in order to simplify the mathematics we have neglected such effects, a refinement of the theory may perhaps be necessary later) Cell cultures irradiated with alpha rays do not show any short time recovery ('Elkind recovery) (ELKIND et coll 1964) We therefore suppose that the α component will only be submitted to an insignificant recovery effect and consequently take $k = 1$ However, for the β component, we choose $k = 5$ for normal cells (i e $kD_{o\beta} = 1\,000$ rad) and $k = 2$ for tumor cells (i e $kD_{o\beta} = 100$ rad) These values may seem somewhat

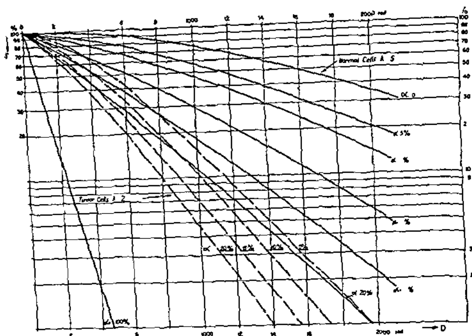


Fig 8 Calculated survival numbers S_v for cells irradiated in vivo as a function of dose for various kind of radiation (see also Tables 1 and 2) The ordinate is logarithmic the abscissa linear

arbitrary (the recovery factor k may also differ greatly for different cells) but they have been chosen to make the survival numbers consistent with the clinical experience

In Tables 1 and 2 as well as in Fig 8, the survivals in vivo are shown for various a values and various doses (single doses) calculated with these parameters

To-day most people agree that recovery effects in vivo are essential for a successful tumor therapy and the importance of the tumor bed, i e the normal cells surrounding the tumor cells, for the results of therapy is generally accepted It has often been mentioned that differences in the recovery of tumor cells and normal cells after radiation damage may improve the selectivity of the radiation (COHEN 1960) Our theory and the values chosen for the recovery factor k give only a mathematical formulation of such ideas The relation between surviving numbers of the normal cells and of tumor cells is shown in Fig 9

With small doses where the α component showing no recovery, is producing the greatest effect this relation is very close to 1 When however the dose is increased for instance above 500 rad the influence of the β component gains

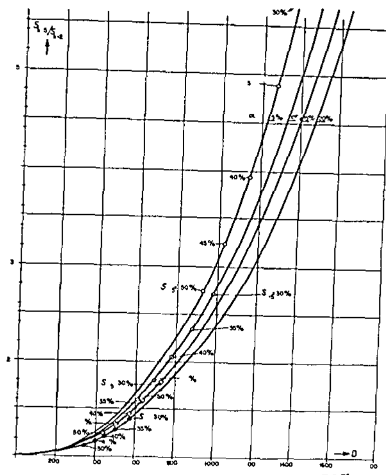


Fig 9 Relation ($\xi = S/S_{\lambda=2}$) between the surviving normal and the surviving tumor cells depending on the magnitude of the single dose The relation (electivity) was calculated with the survival numbers shown in fig 8 and Tables 1 and 2 The curves show the calculated electivity for various quota a of the a component Survival numbers from 30 to 50 for irradiated normal cells are marked on the curves Ordinates and abscissa linear

in importance and the electivity relation will increase With $a = 5$ % (irradiation with 30 MeV electrons), a dose of 1 000 rad gives an electivity relation of 3 1, where is higher a values result in a somewhat smaller electivity When comparing the values for the various types of radiation however, we have to pay due attention to the fact that the size of the applicable single doses is limited because of the tolerance of the patient The number of surviving normal cells after irradiation may be taken as a limit for the size of dose that can be applied If this number drops below, let us say 30 to 50 %, the repopulations of the tissue with new cells, in the interval between two irradiations, may be insufficient and thus result in a non tolerable radiation damage

Table 3

Factor of electivity $S_{k=5}/S_{k=2}$ as a function of dose (D) for various values of α and the same parameters as for tables 1 and 2

α	D =	100	200	300	500	1 000	1 200	1 500	2 000 rad
5	$S_{k=5}/S_{k=2}$ =	1 008	1 0 2	1 136	1 419	3 08	4 3	7 12	15 2
10	=	1 0075	1 042	1 120	1 372	2 78	3 77	5 92	13 4
15	=	1 007	1 029	1 105	1.33	2 55	3 43	5 12	11 3
0	=	1 006	1 032	1.091	1 29	2 38	3 05	4 69	8 95

In Fig 9 (see also Table 3), we have marked on the curves the dose values for which we get 30 to 50 % surviving normal cells If we take, for example, 40 % as a limit the maximum permissible single dose will be 1 150 rad for high energy electrons ($\alpha = 5$ %), giving an electivity relation of nearly 4, whereas 200 keV roentgen rays ($\alpha = 15$ %) will allow of only a 570 rad single dose to be given which results in an electivity of only 1 45

These results very clearly disclose two facts first the important therapeutic advantages of high single doses, and secondly the benefit of therapy with high energy electrons Single doses of 300 rad are used quite often In this case, the electivity is only 1 2 and the recovery effects of the normal cells are then of little influence because most of the cells are sterilized by the α component of radiation In Tables 1 and 2, also the relations of the cells killed by *the β component* are quoted i e $(1-S_\beta)$ *to those killed* by the α component i e $(1-S)$ If we use a single dose of 300 rad the relation $\frac{1-S_\beta}{1-S}$ for normal cells is only 2 04 % for $\alpha = 20$ % and 10 8 % for $\alpha = 5$ %, thus showing that in *these cases the influence* of the α component predominates A single 1 200 rad *dose of high* energy electrons ($\alpha = 5$ %) will in contrast give a relation *of 70 % and in this case the β* component can certainly not be disregarded

At the body depth of the tumor where *most of the high* energy electrons have been attenuated to lower *energies, the α* value will be higher of course and the α component will thus have a greater influence For $\alpha = 10$ % a single dose of 1 200 rad for instance will give a relation $\frac{1-S_\beta}{1-S}$ of 41 5 % for normal cells and 116 % for tumor cells

We will now discuss the relative numbers of surviving tumor cells for various radiations and treatment *plans* The numbers of surviving tumor cells with a single dose of 200 rad *and also for $n = 30$* single doses given ($D_{total} = 6\,000$ rad) as fractionated *treatment for* various values of α, are given in Table 4

Table 4

Survival rate (S_Σ) for tumor cells with a recovery factor $k = 2$ for various values of α and a single dose of 200 rad and also 30 separate doses of 200 rad (total dose 6 000 rad) — Parameters are the same as for tables 1 and 2

	$\alpha = 5$	10	15	20 %
$D_1 = 200$ rad	$S_\Sigma = 85.6$	78.0	71.7	64.6 %
$D_{total} =$ $30 \times D_1 =$ 6 000 rad	$S_\Sigma = 942 \cdot 10^{-5}$	$47.8 \cdot 10^{-5}$	$4.63 \cdot 10^{-5}$	$0.203 \cdot 10^{-5}$

With 200 keV roentgen irradiation ($\alpha = 15$ %) a total dose of 6 000 rad is used in many cases, and we will therefore take the survival number $S_\Sigma = (0.717)^{30} = 4.63 \cdot 10^{-5}$ for this case as a typical end point for classical radio therapy (this does of course not exclude the fact that a still smaller number of tumor cells would be very desirable). The fractionation number n is now easy to calculate as well as the total dose $n \cdot D_1$ which, using high energy electron therapy with $\alpha = 10$ %, will give the same survival figure ($4.63 \cdot 10^{-5}$) of tumor cells for various single doses. These values are shown in the upper line of Table 5. If the single dose is 200 rad, the total dose with electron therapy should be 8 040 rad, and this value corresponds very well with to day's practice. Single doses of 1 200 rad give a total dose of 4 170 rad, in good agreement with SCHUMACHER's experiences (1964). The calculated values in Table 5 show exactly the same trend as the total doses found experimentally by STRANDQVIST (1944) with fractionated irradiation of skin and squamous carcinoma cells using conventional roentgen irradiation.

The calculated survivals will of course not apply to anoxic tumor cells. The oxygen effect will change the sensitivity of the cells with regard to the β component whereas the influence of the α component will probably change very little. — Measurements on cell cultures show (according to BARENDSEN 1964) that the D value for ^{210}Po alpha rays will increase only 18 % for cells in nitrogen, as compared to cells in air. Measurements in vivo are lacking. — If we assume that the killing by the α component remains unchanged, whereas the D-value for the β component increases by a factor of 2.5 for anoxic cells, we will get the same survival numbers for the anoxic tumor cells as previously calculated for normal cells (Table 1). The criterion for the survival number of the anoxic tumor cells with 200 rad single dose and $\alpha = 15$ % (i.e. conventional roentgen therapy) will then be $S_\Sigma = (0.738)^{30} = 11.01 \cdot 10^{-5}$, and using this value we now get much higher values for the fractionation numbers n and for the

Table 5

Number of irradiations (n) and total dose (D_{total}) necessary to reduce the surviving tumor cells to a fraction of 4 63 10^{-5} for oxygenated cells with a recovery factor k = 2 and to 1 10 10^{-4} for anoxic tumor cells having k = 5 (D_1 is the single dose given) — Parameters same as for previous tables

k =	D =	100	200	300	500	1 000	1 200	1 500	2 000 rad
	n =	97 7	40 2	23 4	11 5	4 44	3 47	2 61	1.57
2	D_{total} =	9 270	8 040	7 020	5 760	4 440	4 160	3 970	3 140 rad
	n =	91 0	44 0	29 05	16.58	7.38	5 91	4.50	3 17
5	D_{total} =	9 100	8 800	8 720	8 290	7 380	7 090	6 750	6 340 rad

total doses D_{total} with electron therapy as before (see Table 5 lower lines) Single doses of 200 rad will for instance give a total dose of 8 800 rad whereas single doses of 1 200 rad result in a total dose of 7 090 rad However we have to remember that only a small part (perhaps only 10 %) of the tumor cells might be anoxic, and the criterion of survival 11 01 10^{-4} is therefore now much stronger and much more difficult to fulfill than the criterion in our previous example for oxygenated tumor cells To-day our experiences with high energy electron therapy using high single doses are still too young to demonstrate the necessity of such high total doses however there are some indications from SCHUMACHER s results that higher total doses must be given to avoid local recurrences In this connection hyperaemic effects e g supervascularisation, with an increased oxygenation caused by the high single dose also have to be taken into the consideration

These few examples show that a two-component theory of radiation considering the recovery effects of cells in vivo can give quantitative explanations and useful answers to many problems in radiation therapy It has to be remembered however that we have used hypothetical parameters for our calculations and in order to develop our hypothesis into a well founded theory those parameters have to be measured

The relation α for various radiations may be relatively easy to measure Rossi s low pressure proportional counter (1961) could be useful calculations of the number of δ-rays may give indications (HUG 1964 ROSSI 1964) (again the lowest energy defining a δ-ray is important) and perhaps also some radiobiologic tests for instance radiation induced chromosome alterations which only show up for the α-component (NEARY et coll 1963) may be helpful Such measurements must be carried out at various depths of a phantom and in future therapy work not only isodose curves but also iso-α-curves will be necessary to characterize the dose field in a body especially when more than one treatment field is used The measurement of the α values is an entirely

Table 4

Survival rate (S_-) for tumor cells with a recovery factor $k = 2$ for various values of a and a single dose of 200 rad and also 30 separate doses of 200 rad (total dose 6 000 rad) — Parameters are the same as for tables 1 and 2

	$a = 5$	10	15	20 %
$D_1 = 200$ rad	$S_- = 85.6$	78.0	71.7	64.6 %
$D_{total} =$ $30 \times D_1 =$ 6 000 rad	$S_\Sigma = 942 \cdot 10^{-5}$	$47.8 \cdot 10^{-5}$	$4.63 \cdot 10^{-5}$	$0.203 \cdot 10^{-5}$

With 200 keV roentgen irradiation ($a = 15$ %) a total dose of 6 000 rad is used in many cases, and we will therefore take the survival number $S_\Sigma = (0.717)^{30} = 4.63 \cdot 10^{-5}$ for this case as a typical end point for classical radiotherapy (this does of course not exclude the fact that a still smaller number of tumor cells would be very desirable). The fractionation number n is now easy to calculate as well as the total dose $n \cdot D_1$ which, using high energy electron therapy with $a = 10$ %, will give the same survival figure ($4.63 \cdot 10^{-5}$) of tumor cells for various single doses. These values are shown in the upper line of Table 5. If the single dose is 200 rad, the total dose with electron therapy should be 8 010 rad, *and this value corresponds very well with to day's practice*. Single doses of 1 200 rad give a total dose of 4 170 rad, in good agreement with SCHUMACHER's experiences (1964). The calculated values in Table 5 show exactly the same trend as the total doses found experimentally by STRANDQVIST (1944) with fractionated irradiation of skin and squamous carcinoma cells using conventional roentgen irradiation.

The calculated survivals will of course not apply to anoxic tumor cells. The oxygen effect will change the sensitivity of the cells with regard to the β component whereas the influence of the a component will probably change very little. — Measurements on cell cultures show (according to BARENDSEN 1964) that the D value for ^{210}Po alpha rays will increase only 18 % for cells in nitrogen, as compared to cells in air. Measurements in vivo are lacking. — If we assume that the killing by the a component remains unchanged, whereas the D_o-value for the β component increases by a factor of 2.5 for anoxic cells, we will get the same survival numbers for the anoxic tumor cells as previously calculated for normal cells (Table 1). The criterion for the survival number of the anoxic tumor cells with 200 rad single dose and $a = 15$ % (i.e. conventional roentgen therapy) will then be $S_- = (0.738)^{30} = 11.01 \cdot 10^{-5}$, and using this value we now get much higher values for the fractionation numbers n and for the

radioprotective drugs such as pyridoxal 5 phosphate, vitamin B_{12} and anabolic steroids) It seems clear that cytostatica could adversely influence the recovery of the normal cells and also depress such immunologic reactions of the body that are specially impor ant for the elimination of metastases This assumption has recently been confirmed clinically An elevated oxygen pressure, and also radiation protective drugs, may on the other hand advance recovery and therefore be helpful (recovery treatment) Such indications will be especially important when high single irradiation doses are used Again we have to remember that quantitative investigations of such effects require exact measurements of cell survival in vivo

Our theory is an attempt to bridge the existing gap between radiobiology and radiotherapy without too much speculation upon the still very hypothetical ideas concerning the primary radiation effects on the macromolecules of the cells It lies of course near at hand to identify the influence of the α component as a hit and injury of the cell nucleus (i e nucleic acids), whereas the influence of the β component probably depends on the accumulation of many single ionization effects causing damage to sensitive structures over the entire cell volume

SUMMARY

Clinical experience shows that survival curves obtained with irradiated cell cultures are not directly applicable to therapeutic irradiations The inconsistency may be due to different recovery effects for conditions in vitro and in vivo For a mathematical investigation radiation is divided into a densely ionizing α-component producing exponential dose effect curves and a sparsely ionizing β-component producing shoulder-curves It is postulated that the 37 % dose for the β-component (linear part of the curve) is increased by a recovery factor k for cells in vivo as compared to cell cultures An example is given showing that curve parameters may be chosen so as to agree with results in vitro as well as with radiotherapeutic experience Therapy with high-energy electrons having only a small part of the α-component (α about 5) gives the best recovery and superior treatment results especially when high single doses, resulting in increased electivity are used

ZUSAMMENFASSUNG

Klinische Erfahrungen zeigen dass die Ergebnisse der bestrahlten Zellkulturen sich nicht ohne weiteres auf die Strahlentherapie übertragen lassen Die Unterschiede lassen sich durch unterschiedliche Erholungseffekte in vitro und in vivo erklären Für eine mathematische Untersuchung wird die Strahlung in eine dicht ionisierende α Komponente und eine spärlich ionisierende β Komponente zerlegt Die α Komponente (Anteil α) erzeugt exponentielle Dosiseffekt Kurven die β Komponente Schulterkurven Es wird postuliert dass die 37 Dosis der β Komponente (im linearen Kurventeil) durch Erholungseffekte in vivo gegenüber die Verhältnisse in vitro um den Faktor k erhöht wird Ein Beispiel zeigt dass die Parameter so gewählt werden können dass die Resultate mit den Zellkulturmessungen und

physical task. However, the definition of the α component for various types of radiation must be based on biological experience and measurements. — In order to explain all experiences with cell cultures, BARENDSEN has proposed to divide the spectrum of radiation into three parts with various LET values: below 20 keV/μ, between 20/100 keV/μ and above 100 keV/μ. — The sparsely ionizing part may correspond with our β component whereas our α component now has been divided into one part that depends on oxygen pressure and cysteamine treatment and another part (LET above 100 keV/μ) that is independent of such influence. When measurements in vivo have been further developed, allowing quantitative measurements of cell survivals, our present theory will perhaps have to be further refined; also tumor growth during the treatment period will have to be considered.

Of equal importance is the quantitative measurement of the biologic effects in vivo. To day, radiotherapists mostly use more or less qualitative indications of the radiation effects (lysis effects on tumors, skin erythema) or some indirect effects (changes in rate of mitosis, (REICHE 1955), changes in chemical cell reactions (ZUPPINGER & MINDER 1962), changes in the mass of an organ (OESER 1962) and change in protein production of the cells). However, such indirect effects may often be influenced also by other causes. Only a reliable and fairly exact method for registering 'survival in vivo' will enable quantitative investigations of recovery effects in vivo to be made.

In our calculations we have treated the recovery effect in a very cursory and simplified way (recovery factor λ). Very probably the recovery may be the result of many complicated phenomena that may depend on time, milieu, cell type, the general condition of the patient, immunologic reactions and, last but not least, on the various parameters of irradiation (we have for instance not mentioned the important and not very well understood influence of the dose rate).

Our philosophy has shown that the phase of recovery in many cases may be decisive for the successful treatment of the patient. The electivity can be increased by a suitable irradiation rythm but certain limits of the single doses must not be surpassed in order to avoid serious radiation injury. Physical problems such as dosimetry, and the planning and application of a suitable dose field are, more or less, trivial problems for the therapist and could in many cases be left to the radiation physicist, whereas the study and investigation of the biologic problems in vivo, mainly the recovery phase and the immunologic reactions, should be the most important fields for the physician.

There are at present many investigators who study the influence and the combined use of chemical agents (cytostatica, enhanced oxygen pressure and the like) on radiation therapy, and also on the recovery phase (injection of

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auch mit den strahlentherapeutischen Erfahrungen übereinstimmen. Hochenergetische Elektronen haben den kleinsten Anteil (~ 5 %) an der α-Komponente. Dies erklärt die gute Erholung nach der Bestrahlung. Wenn hohe Einzeldosen verwendet werden, steigt die Elektivität der Bestrahlung und die therapeutische Ergebnisse werden besser.

RÉSUMÉ

L'expérimentation clinique montre que les courbes de survie des cultures de cellules irradiées ne sont pas directement applicables aux irradiations thérapeutiques. On peut expliquer cette discordance par une différence des effets de restauration in vitro et in vivo. Pour traiter ce problème de façon mathématique on divise les radiations en deux groupes: une composante alpha à haute densité ionisante donnant des courbes exponentielles de l'effet en fonction de la dose, et une composante béta à faible pouvoir ionisant donnant des courbes en forme d'épaulement. L'auteur émet le postulat suivant: la dose constante D_0 (pour 37 % de survivants) pour la composante béta (partie linéaire de la courbe) est multipliée par un facteur de restauration λ pour les cellules in vivo par rapport aux cultures de cellules. Il donne un exemple montrant qu'on peut choisir les paramètres de courbes de façon que les résultats in vitro correspondent avec l'expérimentation thérapeutique. Les électrons de grande énergie n'ont qu'une très faible composante alpha, environ 5 %. Ceci explique qu'ils permettent une meilleure restauration et donnent des résultats thérapeutiques supérieurs, en particulier quand on donne une forte dose unique qui augmente l'électivité de l'irradiation.

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FROM THE DEPARTMENT OF PATHOLOGY II (DIRECTOR PROF S FALKMER) AND THE DEPARTMENT OF RADIOTHERAPY (DIRECTOR PROF L C LARSSON), UNIVERSITY OF UMEÅ SWEDEN

MICROANGIOGRAPHIC STUDIES ON CHANGES IN THE CEREBRAL VESSELS AFTER IRRADIATION

I Lesions in the rabbit produced by ^{60}Co γ rays, 195 kV and 34 MV roentgen rays

by

O HASSLER and A MOVIN

Several previous investigators (cf SCHOLZ 1934 BERG & LINDGREN 1958) in dealing with radiation lesions in the brain have suggested that changes in the vessels may be primary to those of the parenchyma Vascular endothelium is said to be more sensitive to radiation than brain tissue (WARREN 1943)

To check the validity of these statements it was thought worthwhile to investigate the reaction of the vessels with recently developed microangiographic methods as these have several advantages over the classical morphologic methods for studying blood vessels in general (BELLMAN 1953 GOTHMAN 1961) and in the brain in particular (HASSLER 1964) With these methods good stereoscopic pictures of minute vessels are obtained and large tissue volumes can be systematically examined It would appear that radiation induced vascular lesions have not been studied previously in this manner

Submitted for publication 8 September 1965

Table

Survey of material, irradiations investigations and results

Rabbit No	Type of radiation	Dose (rad)	Time betw irrad and death (days)	Investigation	Haemorrhages[1]	Necrosis[1]	Telangiectases[1]
1	Roentgen rays (195 kV)	2 300	30	Peroxidase	—	—	—
2	»	2 300	30	»	—	—	—
3	»	2 300	90	»	+	—	—
4	»	2 300	90	Microradiogr	+	—	
5	»	2 300	127	Peroxidase	++	—	+
6	»	2 300	180	»	+	—	+
7	»	2 300	180	»	+	—	+
8	»	2 300	218	»	+++	+	++
9	»	2 300	270	»	+	++	++
10	»	2 300	270	Microradiogr	+	++	+++
11	»	2 300	360	Peroxidase	+	+	+
12	»	2 300	360	»	+	+++	++
13	γ rays (^{60}Co)	2 300	1	»	—	—	—
14	»	2 300	2	»	—	—	—
15	»	2 800	10	»	—	—	—
16	»	2 300	20	Microradiogr	—	—	—
17	»	2 300	20	Peroxidase	—	—	—
18	»	2 300	30	»	—	—	—
19	»	2 300	30	»	—	—	—
20	»	3 300	60	»	+	—	—
21	»	7 400	60	»	+	++	—
22	»	2 800	90	»	—	+	—
23	»	2 300	90	»	+	—	—
24	»	2 300	90	»	+	—	—
25	»	2 300	180	»	+	—	—
26	»	2 300	180	»	++	+	+
27	»	2 300	180	»	+	+	++
28	»	2 300	196	Microradiogr	+	+++	+++
29	»	2 300	218	Peroxidase	+++	++	++
30	»	2 300	270	»	+	++	++
31	»	2 300	270	Microradiogr	+	++	+
32	»	2 300	298	Peroxidase	++	++	++
33	»	2 300	360	»	+	++	++
34	»	2 300	360	»	+	++	+
35	Roentgen rays (34 MV)	2 100	30	Peroxidase	—	—	—
36	»	2 100	30	»	—	—	—
37	»	2 100	90	»	+	—	—
38	»	2 100	90	»	+	—	—
39	»	2 100	180	Microradiogr	+	—	—
40	»	2 100	180	Peroxidase	+	—	—
41	»	2 100	180	Microradiogr	+	—	—
42	»	2 100	270	Peroxidase	++	—	+
43	»	2 100	270	»	+	+	++
44	»	2 100	270	»	++	++	+
45	»	2 100	360	Microradiogr	+	+	+
46	»	2 100	360	Peroxidase	+	++	+
47	»	2 100	360	»	+	++	++

For footnote belonging to this table see opposite page

Material Forty seven rabbits weighing 1 5 to 2 0 kg at the time of irradiation were used The material was divided into 3 groups according to the type of radiation administered (see Table) The animals were kept in individual cages after irradiation and fed rabbit chow and water ad lib

Irradiation After the intravenous injection of a barbiturate (30 mg/kg body weight of Mebumal, from ACO Stockholm), the animals were irradiated on the left side of the skull up to the midline, the anterior limit of the field being placed in line with the posterior canthus of the eye The rabbits were carefully watched during the whole irradiation If the animal happened to move, the irradiation was immediately arrested and not continued until the head had been again adjusted

The first group was treated with 195 kV roentgen rays FSD 50 cm, filter 0 5 mm Cu and 1 mm Al, field size 2 5 × 2 5 cm, exposure 2 850 R (All radiation sources were calibrated with Fricke dosimeters) The dose in the brain 1 cm beneath the skin was calculated to be about 2 300 rad (Depth Dose Tables for Use in Radiotherapy) (JOHNS 1961)

The second group was treated with * Co radiation from a kilocurie therapy unit FSD 60 cm no filter field size 2 0 × 2 0 cm The field was primarily screened off with the ordinary diaphragm and a secondary lead screen was also used in order to reduce the penumbra The exposure in the centre of the field was in most instances 2 960 R and 3 mm outside the field it was 245 R The dose in the brain 1 cm beneath the skin was then calculated to be about 2 300 rad (see Clinical Dosimetry 1963)

The third group was treated with 34 MV roentgen rays from a betatron field size 2 0 × 2 5 cm The treatment was given through a bolus which was homogenous tissue equivalent and 1 5 cm thick The dose 1 cm beneath the skin in the central parts of the field was calculated to be about 2 100 rad (HETTINGER, personal communication) (It was planned to give these animals

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The degree of haemorrhages was classified in the following way
+ + + Total volume of macroscopically visible haemorrhages > 1 mm
+ + Total volume of macroscopically visible haemorrhages < 1 mm and/or brownish haemosiderin pigment
+ Haemorrhages visible only microscopically
The degree of necrosis was classified in the following way
+ + + Total volume of necrotic cysts > 1 mm³
+ + Total volume of necrotic cysts < 1 mm or a shrunken appearance
+ Necrotic changes only visible microscopically
The degree of telangiectases was classified into
+ + + Total length of the telangiectases in one brain > 1 mm
+ + Total length of the telangiectases in one brain 0 1—1 mm
+ Total length of the telangiectases in one brain < 0 1 mm

a tissue dose of 2 300 rad at 1 cm depth, later corrections of the betatron dosimetry revealed, however, that only 2 100 rad had been administered)

Microangiographic examination This was performed either by the peroxidase or the microradiologic method (see Table) The former is based on erythrocyte staining of thick frozen sections When the latter is used, the vascular system is at first filled with fine grained barium sulphate, and thick tissue slices are then examined with microradiography Both methods were described in detail in a previous communication (HASSLER 1964)

Histologic examination The specimens were embedded in paraffin and sections stained by Gomori's elastin and by Ladewig's, Nissl's and van Gieson's methods The opposite, non irradiated hemisphere was investigated by the same morphologic methods as the irradiated side and served as a control in each case

The semiquantitative grading used for the lesions is described in a footnote to the Table The volumes were calculated after measurements with a micro meter in the ocular plane of a dissection microscope The length of the telangi ectases was measured directly in the angiogram

Results

Gross observations After irradiation the animals gained weight moderately and none weighed less than before the irradiation when it was killed or it died Four rabbits (Nos 5, 8, 29, and 32) died spontaneously, but the brain could be fixed within 14 hours post mortem and examined with the peroxidase method All of the animals irradiated with conventional roentgen rays develop ed a temporary epilation of the irradiated skin over the crown The epilation occurred mainly 30 to 60 days after the irradiation Ten animals (Nos 8, 10, 12, 28, 29, 31, 32, 33, 45, 47 in the Table) had various neurologic signs (ami socoria, vestibulo cerebellar signs wry neck) and in No 45 epileptic seizures as well

No gross changes were evident in the meninges except in animal No 45, in which a tumour had destroyed the bone of the skull, infiltrated the meninges and caused an impression in the brain The surface of the irradiated parts of the brain of some animals had a slight brownish discoloration probably from haemosiderin pigment Haemorrhages and necrotic cysts were often observed when the brains were cut into slices (cf Table)

Microangiographic examination The results are compiled in the Table No distinct changes in the angioarchitecture were observed 1 to 90 days after the



a



b

Fig 1 a) M croang gram of a 2 mm thick sl ce from the bra n of rabbit No 28 Nec o s and telangı cta es ma nly n the white m tter on rradiated left s de × 4 b) Enlarged det l t demonstrate the telang ectases and necro ıs × 16

a tissue dose of 2 300 rad at 1 cm depth, later corrections of the betatron dosimetry revealed, however, that only 2 100 rad had been administered)

Microangiographic examination This was performed either by the peroxidase or the microradiologic method (see Table) The former is based on erythrocyte staining of thick frozen sections When the latter is used, the vascular system is at first filled with fine grained barium sulphate, and thick tissue slices are then examined with microradiography Both methods were described in detail in a previous communication (HASSLER 1964)

Histologic examination The specimens were embedded in paraffin and sections stained by Gomori's elastin and by Ladewig's, Nissl s and van Gieson s methods The opposite, non irradiated hemisphere was investigated by the same morphologic methods as the irradiated side and served as a control in each case

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Fig 3 Peroxidase stained frozen section 300 μ thick Capillary angioarchitecture at the margin of a radiation lesion in rabbit No 47 The cerebral cortex (upwards) is well preserved the telangiectases occurring mainly in the white matter (downwards) which is partly necrotic × 85

The telangiectases occurred almost exclusively in the white matter Only in rabbits 10 28 and 30 were they observed both in the grey and the white matter but were then more marked in the latter The lesions in the irradiated brains with no tissue necrosis were most marked in the white matter along the central beam The telangiectases were especially well developed in the neighbourhood of the lateral ventricles and the base of the brain When necrosis occurred in the centre of the radiation lesions the telangiectases were found at the transition between the necrosis and the normal brain tissue No distinct differences between the various types of radiation could be observed with regard to the localization or appearance of the lesions except that the changes were a little less marked in the animals irradiated with the 34 MV roentgen beam



a b

Fig 2 a) Histologic section from the area with telangiectases in fig 1 Elastin van Gieson s stain × 80 b) Section through the tumour of rabbit No 45 Osteogenic sarcoma rich in moderately atypical cells with abundant formation of atypical osteoid bone trabeculae Van Gieson s stain × 190

irradiation After 90 days or more, small petechial haemorrhages were an almost constant finding in the irradiated brain areas The haemorrhages occurred both in areas with telangiectases and in those with apparently normal angiographic appearances No petechial haemorrhages occurred in the opposite control hemisphere

Slight telangiectases were observed 127 days after the irradiation When these were small, it was difficult to exclude regional, irregularly occurring vascular dilatation due to circulatory disturbances resulting from petechial haemorrhages or focal oedema Petechial haemorrhages and oedema were frequently observed in the animals killed 30 to 90 days after the irradiation, though no telangiectatic widening was observed Well developed telangiectases (Figs 1 and 2) were first observed 196 days after the irradiation The largest telangiectases were evident nine months after irradiation After one year they were generally slightly smaller than after 9 months

received a fractionated dose of radiation (10 500 R/30 days 200 kV roentgen rays) Both tumours of BERG & LINDGREN and the present tumour were found 360 days after the irradiation

It was not possible to decide whether the telangiectases observed and other vascular changes were primary or secondary to the parenchymatous changes The findings in the present study are more thoroughly discussed in the second work of this series (HASSLER)

SUMMARY

Forty seven rabbits received a moderate dose of γ rays or 195 kV or 34 MV roentgen rays to a field covering one cerebral hemisphere After 1 to 360 days the brains were studied by microangiographic methods to determine the relationship between vascular and parenchymatous changes

ZUSAMMENFASSUNG

Siebenundvierzig Kaninchen erhielten eine massige Dosis γ Strahlen oder 195 kV oder 34 MV Röntgenstrahlen auf ein Feld welches eine Grosshirnhemisphare deckte Nach 1 bis 360 Tagen wurden die Gehirne mit modernen mikroangiographischen Methoden untersucht um den Zusammenhang zwischen Gefassveranderungen und Veranderungen im Parenchym festzustellen

RÉSUMÉ

Quarante sept lapins ont été irradiés sur un champ couvrant un hémisphère cérébral par une dose modérée de rayons gamma ou de rayons de roentgen de 195 kV ou 34 MV Leurs cerveaux ont été etudiés apres 1 a 360 jours par des méthodes microangiographiques pour déterminer les relations entre les lésions vasculaires et les lésions parenchymateuses

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CAVENESS W F ROIZIN L INNES J R M and CARSTEN A Delayed effects of x irradiation on the central nervous *system of the monkey In* Response of the nervous system to ionizing radiation p 448 Edited by T J *Haley* and R S Snider Little Brown & Co Boston 1964

Routine histologic examination Changes in radiation lesions were evident (cf BERG & LINDGREN) and were mainly located to the white matter A slight swelling of the endothelial cells and a fibrinoid staining of the vessel wall was sometimes observed in areas with normal angiographic appearances An oedematous separation of the brain parenchyma around these vessels was as a rule observed Loss of the normal architecture was common When necrosis occurred (see Table) this was accompanied by cystic degeneration with surrounding marked gliosis The telangiectases had extremely thin walls which were made up only of endothelium and small amounts of collagenous connective tissue Smooth muscle and elastic tissue were absent When telangiectases occurred, necrosis, or in four rabbits (Nos 5, 6, 7, and 42) marked tissue changes of the above mentioned type were evident Sections through the tumour from rabbit 15 revealed an osteosarcoma rich in cells with moderate cell atypia and abundant formation of atypical, osteoid bone trabeculae (Fig 2)

Discussion

Although telangiectases have been mentioned by many authors (cf BERG & LINDGREN 1958), it is not possible to obtain information from the literature exactly when these appear and how they develop In the case of slight telangiectases, the diagnosis based solely on histologic sections is unreliable because the changes cannot be adequately separated from physiologically dilated, thin walled veins The present study indicates that they do not arise until 4 to 6 months after a 'therapeutic' irradiation dose, a finding which is in conformity with numerous reports It is common to divide radiation reactions into 'early' and 'delayed' (cf BROWNSON et coll 1964), the telangiectases belonging obviously to the latter Because some of these delayed effects may be observed 4 weeks after irradiation similar to that in the present study (CAVENESS, ROIZIN, INNES & CARSTEN 1964), the telangiectases seem to be late delayed effects and may be secondary to some earlier delayed effects, e g degenerative and inflammatory glia cell changes (CAVENESS et coll)

No distinct differences could be found between the various kinds of radiation used The reason why the 34 MV roentgen irradiated animals had slightly less marked changes may well be due to the fact that they had received a slightly lower radiation dose

The tumour observed in the irradiated area of rabbit No 15 resembled histologically the two osteogenic sarcomas reported by BERG & LINDGREN One of the rabbits of these authors received a dose of radiation (2 500 R single dose, 200 kV roentgen rays) similar to our rabbit whereas the other

FROM THE RADIUM CENTRE FOR JUTLAND (PROF S KAAE), ARHUS DENMARK

ACUTE GASTRIC ULCERS INDUCED BY RADIATION

by

A SELL and T SKOV JENSEN

Gastric lesions as complications in high voltage radiotherapy have become of interest in recent years particularly in the treatment of malignant tumours of the testis This communication is concerned with four cases of acute gastric ulceration observed following postoperative irradiation of the lumbar lymph nodes in malignant testicular tumours

Various forms of gastric lesions following external irradiation have been reported especially from the Walter Reed General Hospital Washington by BRICK (1955) HAMILTON (1947) FRIEDMANN (ref 9), PALMER (1948) and WARREN (1942) FRIEDMANN described four types of gastric damage in a series of about 250 malignant testicular tumours (1) dyspepsia (2) gastritis, (3) late chronic ulcer and (4) acute ulcer with or without perforation

1 Radiation induced dyspepsia — to be distinguished from the common roentgen kater occurring during the treatment — arises 6 months to 4 years later as vague gastric symptoms without clinical or radiologic signs

2 Radiation *induced gastritis sets in earlier than the* dyspepsia, as a rule 1 to 12 months after the completion of radiotherapy and is accompanied by radiologic evidence of spasm or stenosis of the antrum Gastroscopy reveals smoothened mucosal folds and mucosal atrophy The pathologic basis is fibrosis of the submucous tissue

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Fig 1 Control rad ography of the f e d l m ts Contrast *filled lymph nodes* are visible in the field

The *gastroscopic* appearances are said to be characteristic (PALMER 1948) The irradiated area, as a rule the *antrum* is transformed into an almost stiff tube, with reduced or absent peristalsis the remainder of the gastric wall being oedematous Where an ulcer is present, it is said to be typically deep and sharp-edged *if it heals* it does so slowly and may leave no scar

Histologic investigations have *not* disclosed any changes that could distinguish radiation induced ulcers from simple ulcers However *it has been* emphasized (WOOD et coll 1963) that irradiation produces particularly marked mucous and submucous oedema as well as vascular changes involving prolif eration of endothelial cells and thickening of the vessel walls The submucous fibrosis and the endarteritic changes are also marked, without being spec ific in late lesions following irradiation

Animal experiments performed inter alios by ENGELSTAD (1938) have revealed lesions following irradiation of the stomach similar to those in man

Present material All testicular tumours referred during the period March 1962 to December 1964 have been treated postoperatively with telecobalt to the para aortic and homolateral iliac lymph nodes A total of 38 patients were treated distributed histologically in 18 pure seminomas and 20 non-semi nomatous carcinomas Prior to radiotherapy all the patients had been sub jected to hemicastration but not to therapeutic or prophylactic lymphadenec tomy of the lumbar nodes

The radiation technique using telecobalt, initiated 2 to 3 weeks after the operation comprised en bloc irradiation of the para aortic lymph nodes through two opposed fields, one ventral and one dorsal, of 200 to 240 cm² at 80 cm FSD The fields extended from the middle of the body of the D11 to S1, the field width being about 10 cm, determined from the lymphographic and urographic findings Irradiation of the major parts of the kidney was avoided as far as it was possbile (Fig 1) Only in patients with definite or probable signs of nodal invasion in relation to one kidney was this organ included in the field After the irradiation of the lumbar lymph nodes the patients received irradiation through a supplementary field to the iliac nodes on the operated side

3 Radiation induced ulceration has its onset from 1 month to 6 years with an average of 5 months after radiotherapy The usual ulcer symptoms are present, but food and antacids usually afford no relief The ulcer is radiologically indistinguishable from an ordinary ulcer, it may heal spontaneously, but submucous fibrosis generally produces antral stenosis FRIEDMANN recommended partial gastrectomy

4 Unlike these late, chronic gastric sequelae, the acute, radiation induced ulcer appears as an early complication, usually manifesting itself a month or two after the radiotherapy has been completed This ulcer is deep and penetrates the layers of the stomach, but perforation into the peritoneal cavity is usually prevented by the omentum, the intestine, or the abdominal wall The symptoms are severe and consist of severe epigastric pain and often gastric bleeding Surgery is advisable before serious complications arise

The severity and frequency of the gastric lesions depend upon the size of the dosage received by the stomach When this exceeds 4 500 R, the incidence of gastric ulcer is 25 to 30 % The higher the dose the more serious the gastric damage leading to penetration and haemorrhage

FRIEDMANN (ref 9) has also mentioned the radiation damage sustained by other structures involved in the radiation, such as the skin, subcutaneous tissue, muscles, small and large intestine, kidneys, spinal cord, and bony tissue Although the tolerance seems to be somewhat higher in the small and large intestine than in the stomach, ulceration as well as annular stenosis due to submucous fibrosis may arise

Only a few other authors have described gastric complications after the treatment of the retroperitoneal lymph nodes SEJOURNE (1952) reported a case of atrophic gastritis without symptoms, which had occurred after repeated irradiation of the upper lumbar lymph nodes MOSIMANN (1959) described a case of ulcer of the body of the stomach arising immediately after the completion of radiation to the lumbar lymph nodes through an abdominal field The depth dose was not stated Conservative treatment was tried but haemorrhage and penetration necessitated operation PIET (1960) reported 4 cases of slight, late gastric lesions in a series of 89 irradiated testicular tumours There is no exact statement of the depth dose, but the skin dose ranged from 2 200 to 3 000 R, delivered through 2 lumbar, convergent fields with 200 kV, 1 mm Cu + 2 mm Al, FSD 50 cm, field size 150 to 200 cm^2 Duodenal ulcer was observed in two cases within one year of the completion of radiotherapy, while deformation of the antrum accompanied by mild dyspepsia was present in two cases These cases were diagnosed 4 years and 6 years respectively, after the treatment WOOD et coll (1963) reported a fatal case of necrotic ulceration of the stomach and intestine after a central dose of 3 000 R, administered in two sittings at an interval of 8 days



Fig 3 Case 2 Operation specimen obtained 2 months later the stomach has been cut along the greater curvature In addition to the ulcer evident in fig 2 two ulcers are present in the first part of the duodenum

with sedatives but recurred in 2 to 3 months they were then severe and included vomiting and weight loss

Urography and *lymphography* failed to reveal signs of metastases in the lumbar lymph nodes. *Roentgen examination* of the stomach disclosed an ulcer in the middle of the lesser curvature Owing to the persistence and severity of the symptoms Polya resection was carried out in December 1963 and revealed adhesions between the organs in the upper abdomen and increased thickness of the gastric wall An ulcer 2 mm deep and 15 mm in diameter was evident on the lesser curvature

Comments After the operation the patient suffered from mild dumping symptoms but has otherwise been in good general health There have been no signs of recurrence Roentgen examination of the large and small intestine 18 months after the treatment demonstrated no signs of stenosing lesions or ulceration and the function of the gastroenterostomy was satisfactory

Case 2 A farmer aged 48 underwent left hemicastration for a testicular seminoma in May 1964 Telecobalt therapy following the operation consisted in a central dose of 4 400 R/35 days (maximum dose 4 900 R/35 days) to the lumbar and right iliac lymph nodes Ten days before the treatment was completed the patient developed pain in the epigastrium accompanied by nausea and vomiting

Roentgen examination disclosed a large prepyloric ulcer crater (Fig 2) Despite medical treatment the symptoms as well as the radiologic signs became more marked and two months later a *Polya resection* had to be carried out because of melaena This revealed three large ulcers all of which were penetrating neighbouring structures (1) an ulcer 3 × 4 cm in size of the anterior wall of the antrum penetrated the anterior abdominal wall (2) two kissing ulcers were evident in the duodenal cap one on the anterior wall about 0 5 to 1 cm in size penetrated to the gallbladder while the other on the posterior wall 2 5 × 3 5 cm in size was



Fig 2 Case 2 Large prepyloric ulcer of the stomach Para aortic lymph nodes filled with contrast medium

The irradiation was administered through one field daily, with a weekly central dose of about 1 000 R and a maximum dose of about 1 100 R As far as the seminomas are concerned, the central dose ranged from 3 500 R/4 weeks to 4 500 R/5 weeks, but with the non seminomatuous carcinomas the average dose was higher, the central dose being about 4 500 to 5 000 R in 4 1/2 to 5 weeks, the maximum dosage about 10 to 15 % higher

This irradiation technique always involves parts of the stomach, transverse colon, and small intestine, apart from the spinal cord The material was analysed with a view to the acute radiation effects upon the stomach, while as yet the late complications cannot be assessed owing to the short follow up time (from 5 to 25 months) for the majority of the patients treated

Three of the 38 treated patients exhibited manifest penetrating gastric ulcers, all of which required surgical treatment, in close relation to the completion of radiotherapy

Case reports

Case 1 Clerk aged 35 who for 10 to 15 years had had periodical dyspepsia without radiologically demonstrable ulcer otherwise in good health In April 1963 the patient had left hemicastration and microscopy revealed malignant testicular teratoma

Postoperatively 4 000 R was administered centrally (maximum dosage 4 300 R) in 35 days to the lumbar and left iliac lymph nodes This was well tolerated without any major dyspepsia but about 2 weeks after its completion the patient developed severe constant pain in the epigastrium similar to that previously experienced The symptoms subsided under treatment

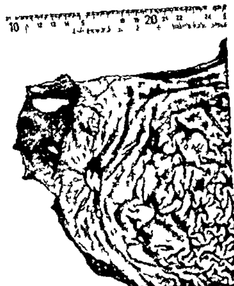


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Fig 4 Case 4 Stomach about 2 months after completion of radiotherapy large ulcer situated close to the greater curvature

firmly adherent to the pancreas (Fig 3) The other abdominal organs were normal Uneventful recovery

Case 3 A mechanic aged 42 previously in good health in November 1964 was subjected to right hemicastration for a testicular seminoma The para aortic and right iliac lymph nodes were irradiated after the operation and received a central dose of 4 500 R/37 days (max dose 4 900 R/37 days)

Towards the end of the treatment the patient developed constant epigastric pain which yielded to food and responded well to antacids Roentgen examination of the stomach revealed an ulcer of the body and gastroscopy confirmed the presence of a sharp edged ulcer 3 × 4 cm in size on the posterior wall of the body After three weeks of conservative treatment the patient had frank melaena and haematemesis which necessitated an immediate Polya resection An ulcer was found on the posterior wall of the body of the stomach penetrating into the transverse mesocolon

Case 4 Moulder aged 21 previously in good health in March 1959 underwent left hemicastration for a malignant teratoma followed by conventional roentgen irradiation to the lumbar nodes 1 600 R in 54 days No dyspeptic symptoms during or immediately after this treatment

One year later the patient was re admitted with constant pain in the left flank and a palpable swelling to the left of the spine

Urography revealed lateral displacement of the left kidney and ureter and the presumed lymph node metastases were irradiated a maximum dose of 4 800 R being administered in 24 days by an arc technique with conventional roentgen rays

Two weeks after the completion of this treatment the patient developed periodical epigastric pain The pain persisted and two months later he was admitted with haematemesis

Roentgen examination of the stomach revealed an ulcer crater in the posterior wall of the stomach close to the greater curvature (Fig 4) The ulcer healed under conservative treatment

Six months later the paitent died with widespred metastases Post mortem revealed a scar 3 mm large, with a flat floor and convergent stellate folds of the mucosa at the site of the treated ulcer the bottom of the ulcer scar was made up of omental tissue which at this site was fibrosed and contained a large vessel

In the first 3 cases now reported upon, there were large ulcers that required surgery, in two because of haemorrhage and in one because of the severity of the symptoms

Arc therapy with conventional roentgen irradiation may also lead to such a high central dose that an acute gastric ulcer results This is exemplified by Case 4 in which the ulcer healed with scar formation during expectant treatment

Histologic examination was carried out in all four cases but no changes that could distinguish the radiation induced ulcers from simple ulcers were evident

Discussion

The dose to the gastric mucosa ranged from 4 000 to 5 000 R/5 weeks in the first three cases of definite ulcers arising in close relation to radiotherapy In the fourth case treated by conventional roentgen rays the dose in the first course of treatment was 1 600 R/54 days and in the second (last) course of treatment it was 4 800 R/24 days These doses are of the same magnitude as those which others have reported in cases of radiation induced ulcers According to FRIEDMANN the tolerance dose in the stomach is about 4 000 R during 5 to 9 weeks, a tolerance dose being taken to be the upper limit which does not entail demonstrable damage acute or chronic

The tolerance limit doubtless varies widely from subject to subject Twenty seven of the 38 patients of the present series received a central dose exceeding 4 000 R/4 to 5 weeks but only three of the group experienced acute symptoms Five patients even received a central dose exceeding 5 000 R and had no symptoms of dyspepsia to demand further investigation It must however be pointed out that the short follow up periods of not more than two years, do not warrant any assessment of the total number of gastric complications

The irradiation includes the stomach in the external irradiation of the regional lymph nodes in malignant testicular tumours The radiosensitivity of the lymph node metastases is extremely varied, but the histologic type affords some guidance In the case of a pure seminoma FRIEDMANN has given the fatal tumour dose as being between 1 500 R/14 days and 3 500 R/4 weeks but large tumours would necessitate an increase in this dose It is also advisable to use a minimum of 3 500 to 4 000 R/4 weeks in those instances of seminomas with considerable cellular atypia or with any suggestion of transition into non seminomatous carcinoma As far as the seminomas are concerned the doses would appear to be within the limit of normal gastric tolerance

The dosage problems are on the whole unsolved in the case of non seminomatous carcinomas However the fatal tumour dose appears to be considerably

higher than for the seminomas, presumably in the range 4 500 to 5 000 R/35 to 40 days (NOTTER & RANUDD 1964) The risk of radiation damage to the stomach and intestine with this sort of dosage is quite high, and the danger should be borne in mind in weighing radiotherapy against lymphadenectomy, or possibly in combining the two in treating non seminomatous carcinomas (MULLER 1962) No random treatment series to afford a consistent answer to these problems has as yet been published

Owing to the close relation of the retroperitoneal lymph nodes to the stomach and other radiosensitive organs, such as the spinal cord and in particular the kidneys, nothing is gained by altering the field technique, e g the multiple field or the arc therapy technique

It is impossible to say whether interstitial irradiation (SEITZMAN et coll 1963), using β emitting isotopes in Lipiodol Ultrafluid (e g ^{124}I, ^{131}I) administered through the lymphatics of the spermatic cord by the usual lymphographic technique, may be useful in the prophylactic treatment of the lumbar and iliac lymph nodes The dose will be insufficient in lymph nodes replaced by tumour tissue, as the latter does not take up the contrast medium Interstitial radio therapy can therefore be considered only for prophylactic purposes or in the presence of micrometastases

The treatment of the acute radiation induced ulcers should presumably be surgical owing to the risk of haemorrhage and perforation This accords with the course in three of the present cases Major palpable swelling in the epigastrium a short time after radiotherapy, possibly accompanied by dyspepsia, should not be interpreted, without further investigation, as nodal metastases, as it may represent a penetrating gastric ulcer with reactive changes in the neighbouring tissues e g the omentum

SUMMARY

Previously reported gastric lesions produced by radiotherapy are briefly reviewed and to these the authors add four cases of gastric ulceration following the irradiation of lumbar lymph nodes associated with malignant testicular tumours The tolerance limit of the normal gastric mucosa was found to be about 4 000 R during 5 to 9 weeks in keeping with the experience of other authors

ZUSAMMENFASSUNG

Die Literatur uber Magenschaden nach Rontgenbestrahlung wird beschrieben Vier Falle von Magengeschwuren wurden vom Verfasser gesehen die Ursache der Geschwure war eine Tiefenbestrahlung von lumbalen Lymphknotenmetastasen bei malignen Hodentumoren Die Toleranzgrenze der normalen Magenschleimhaut liegt bei 4 000 R/5 bis 9 Wochen wie das auch von anderen Autoren festgestellt werden konnte

RÉSUMÉ

Les auteurs passent rapidement en revue les cas déjà publiés de lésions gastriques causées par la radiothérapie et y ajoutent 4 cas d ulcération gastrique après irradiation de ganglions lymphatiques lombaires dans des tumeurs malignes du testicule Ils ont constaté que la limite de tolérance de la muqueuse gastrique normale est d environ 4 000 R en 5 à 9 semaines ce qui est en accord avec l expérience d autres auteurs

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FROM THE DEPARTMENT OF THORACIC RADIOLOGY (DIRECTOR BJORN NORDENSTROM), KAROLINSKA SJUKHUSET, STOCKHOLM

SELECTIVE CATHETERIZATION WITH TIFOCYL INJECTION OF BRONCHOMEDIASTINAL ARTERIES IN BRONCHIAL CARCINOMA

by

BJORN NORDENSTROM

Regional perfusion or intermittent injection of cytostatics in different parts of the vascular system has earlier been attempted It has been shown that regional fractionated injection of nitrogen mustard compounds in vessels *to* malignant tumours resulted in regression of the latter and alleviation of pain (KLOPP et coll) The production of stasis in the efferent vein even increased the effect The substances that are toxic to malignant tissue are still, however, markedly lethal to normal tissue Arterial injection, or the infusion of anti carcinomatous agents, however, are considered by many to represent a promising field in cancer therapy Appreciable advances have been made in *recent years in the endeavour to produce better preparations, but the results* of treatment are still modest

Extracorporeal circulation began to be used in about 1950 for the continuous pumping of anti carcinomatous substances into tumour regions (RYAN et coll , CREECH JR et coll) SULLIVAN et coll (1958) reported that a simple intra arterial infusion technique *could also* be used Various *infusion or perfusion*

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techniques have subsequently been developed for the treatment of tumours in the extremities intestine, liver, pelvis lungs, salivary glands, prostate and orbit (KLOPP et coll, BARBERIO et coll, SULLIVAN et coll, DUFF et coll)

Cannulas have been inserted *in the pulmonary* artery and vein for the perfusion of the lung in cases of bronchial carcinoma This technique does not seem to have been applied to any great extent and should only be considered when radical operative removal of the tumour is impossible The chance of reaching the cells in the interior of the *tumour in this way with cytostatics* is somewhat remote

Histologic investigations of bronchial carcinomas often reveal pathologic vessels from the bronchial arteries in these tumours (BIGNALL, FRIED et coll)

The prerequisite conditions and a *technique for selective catheterization* with angiography of the bronchomediastinal arteries are reported elsewhere by the present author Angiography of the bronchial arteries made it possible to demonstrate an increased number of irregular probably pathologic vessels in a tumour in one patient It was also possible *to* keep the catheter continuously in the bronchial artery for 92 hours for the intermittent administration of nitrogen mustard (Tifocyl) It was, however not possible to carry out any histologic examination of the tumour

An account is now given of a further two cases of *intermittent injection* of cytostatics in the bronchial artery in which it was afterwards possible to make histologic examinations of the tumours

Method The technique of catheterization has been the same as that previously described by the author Thoracic aortography has been performed during temporary occlusion of the thoracic aorta with a balloon catheter to afford a survey of the bronchomediastinal vascular *trunks and has been followed* by selective catheterization of the bronchomediastinal artery The contrast medium was 10 to 15 ml Urografin 60 %, and the cytostatic agent, a nitrogen mustard compound (Tifocyl Astra) in a dose of 10 mg dissolved in 10 ml Urografin 60 % for each injection *The mixture of Tifocyl with a contrast* medium enabled the observation that Tifocyl entered the bronchial artery

The histologic diagnosis before and after the treatments were made at the *Institute of Pathology* (S DAHLGREN)

Case reports

Case 1 Woman aged 40 with a 4 week history of bouts of fever was found to have a tumour in the right upper pulmonary lobe Bronchoscopy disclosed that the carina was broadened but no other changes were evident Transthoracic needle biopsy during roentgen television control yielded malignant cell material As the right hilar glands appeared to be enlarged it



Fig 1 Case 1 a) The bronchomediastinal arteries following aortography with temporary balloon occlusion b) Selective catheterization and injection of an intercostal artery No definite filling of the bronchial artery is evident but a number of mediastinal arteries have been filled

was decided to try the effect of local administration of Tifocyl via the bronchial artery before operation

A general view of the bronchomediastinal arteries after the injection of contrast medium close to the left subclavian artery after temporary balloon occlusion of the thoracic aorta is given in Fig 1a The intercostal and some bronchial arteries seem to be normal in size

A catheter was introduced into an intercostal artery and following injection several mediastinal and intercostal arteries were outlined but no definite filling of the right bronchial artery was evident (Fig 1b)

The catheter was then manipulated into the left superior intercostal artery and small mediastinal vessels intercostal arteries and a bronchial artery to the left inferior lobe were injected (Fig 2)

The catheter was then introduced into the right bronchial artery (Fig 3) into which 10 ml Urografin 60 % and 10 mg Tifocyl were twice injected The central part of the right bronchial artery seemed to be normal in size and course The tumour in the upper lobe and probably a lymph node in the upper part of the right hilum were richly supplied by probably pathologic vessels of different widths

The catheter was left in situ with a heparin drip until the following day The patient s temperature had then risen from 37 C to 38 C but in spite of this a further injection of 10 mg Tifocyl dissolved in 6 ml Urografin 60 % was made into the bronchial artery After 24 hours when the catheter had remained in situ in the bronchial artery for about 48 hours the rectal temperature had risen to 40 C no further Tifocyl was therefore injected and the catheter was removed

The body temperature in the course of the next 48 hours then returned to normal despite the fact that Tifocyl was administered intravenously in a dose of 10 mg per diem this was continued until the operation 5 days after the first Tifocyl injection into the bronchial artery



Fig 2 Same case as in fig 1 a) The pos tion of the catheter having been changed the left super or intercostal artery is catheter ed A number of small arterial branches n the mediastinum and a part of the left bronch al artery are filled b) The catheter has been introduced nto the right bronchial a tery which appears to be norm l n s ze Numerous t rtuous vessels run from the artery to the tumour Th cathet r w s left in pos t on w th a heparin drip for 48 hours during wh ch per od cont ast m dium with Tifocyl was also introduced

and thereafter during 8 days of the postoperative period There were no signs of complications due to the treatment

Operation revealed the presence of metastases in the right hilar lymph nodes and in the mediastinum above the hilum and under the carina Tumourous tissue was also growing into the superior vena cava Right pneumonectomy was performed

Examination of the right lung immediately after its removal revealed that the greater part of the bronchial tumour was necrotic the necroses extending into the surrounding lung tissue Most of a right hilar lymph node about the size of a walnut was necrotic Two further lymph nodes were apparently invaded but had not broken down

Histologic examination revealed that the tumour consisted of a low-differentiated in part solid carcinoma with squamous cell differentiation with regressive changes and necroses extending to the apparently normal lung tissue In some areas viable cancer cells were growing diffusely out into the parenchyma similar carcinomatous structures were present in the accompanying lymph nodes

Case 2 Man aged 65 with an infiltration in the right hilum at mass roentgen examination A tumour 8 × 10 × 10 cm in size lay in the right upper lobe above the hilum and adjacent to the mediastinum A considerably irregular narrowing of the right main bronchus was present The bronchoscopist found marked indentation of the right tracheal wall compression of the right main bronchus and a markedly deformed and fixed carina Examination of the biopsy material revealed the presence of a small-cell undifferentiated bronchial carcinoma

As the tumour was inoperable selective administrat on of Tifocyl to the tumour was tried Aortography with temporary occlusion of the aorta with a balloon catheter was performed and 50 mg Tifocyl were administered with the contrast medium This was followed by the selec



Fig 3 Case 2 Undifferentiated bronchial carcinoma The bronchial artery is widened centrally and bent and displaced medially and backwards by the tumour A large number of small pathologic vessels are present in the tumour Tifocyl injections were given through the catheter for 7 days.

tive catheterization of the right bronchial artery The catheter in Fig 3 lies in the right bronchial artery the central part of which is rather wide A medially displaced bronchial artery, probably normal in width branches off to the lower lobe bronchus which is displaced backwards (3b) Small irregular vessels run from the bronchial artery to the tumour

Tifocyl 10 mg were then administered with the contrast medium and the catheter was left in situ with a heparin drip 10 mg Tifocyl in 10 ml contrast medium thereafter being injected every day for 7 days Thus 70 mg Tifocyl in all were run into the right bronchial artery

There was no temperature reaction during the first 24 hour period The patient then became subfebrile until the 6th day when the temperature rose to 39 C no further Tifocyl was given and the catheter was removed The temperature continued to rise during the subsequent 4 days Antibiotics had no effect upon the temperature and the patient died During the period of administration of Tifocyl the number of thrombocytes sank from 280 000 to 150 000 the day before the patient died while the total number of white blood corpuscles rose during the same period from 7 700 to 14 000

Autopsy disclosed that the pleural cavities contained no increased amount of fluid the parenchyma was markedly engorged and edematous no evidence of bronchopneumonia A tumour about the size of a mandarin was present in the right upper lobe bronchus it was markedly necrotic throughout Small regions with probably viable cells were present but no macroscopically definable vital border zone was evident The tumour extended per continuetatem in the regional lymph glands along the main bronchus There were also free lymph node metastases below the carina and higher up along the trachea the bronchi were dilated and filled with mucus Other observations at autopsy were signs of infection of the spleen and hepatic stasis while the surfaces of the kidneys were scattered with pin sized foci of yellowish colour probably due to interstitial focal nephritis

Microscopic examination of the tumour revealed a low-differentiated necrosed squamous cell carcinoma with necrotic regions extending as far as to normal lung tissue

In connection with the autopsy cultures were made from the lungs as there was a possibility of sepsis Only sparse growths of pseudomonas aeruginosa B subtilis and Klebsiella pneumoniae were evident

Discussion

The cases described and an earlier reported case have shown that it is possible selectively to catheterize the bronchial artery and to leave the catheter in the vessel for several days This seems to open up a possibility of intermittent injections or perfusion of the bronchial arteries with cytostatics or other drugs The rise in temperature in connection with the local injections of Tifocyl may very well have been caused by the occurrence of necrosis in the tumours

The remarkable distribution of the necrotic parts in the tumour is of particular interest The frequent spontaneous necrosis in malignant tumours usually occurs in their central parts Necrosis in the present two cases was however present also in the peripheral parts of the tumour and close to what was considered normal lung tissue This may perhaps indicate that the injections of Tifocyl and the presence of the catheter in the bronchial artery played a role in the occurrence of the necroses

SUMMARY

Two cases of bronchial carcinoma in which selective catheterization with angiography of the bronchial artery and intermittent injections of nitrogen mustard (Tifocyl) were performed are reported Angiography demonstrated pathologic vessels in the tumours in both cases The catheter was left in situ in the bronchial artery for two and six days respectively Extensive necroses occurred in the tumours a short time after the termination of the treatment

ZUSAMMENFASSUNG

Zwei Falle von Bronchialkarzinom werden beschrieben bei denen selektive Angiographie der Bronchialarterien vorgenommen wurde mit nachfolgender wiederholter Injektion von Senfgasverbindungen (Tifocyl) Die Angiographie demonstrierte abnorme Gefässe in beiden Tumoren Der Katheter wurde in der Bronchialarterie zwei bzw sechs Tage liegen gelassen Extensive Tumornekrosen kurz nach Abschluss der Behandlung wurden in beiden Fallen gesehen

RESUMÉ

Présentation de deux cas de cancer bronchique soumis a un cathétérisme électif avec angiographie de l artere bronchique et injection intermittente de moutarde azotée (Tifocyl) L angiographie a montré dans les deux cas des vaisseaux pathologiques dans la tumeur Le catheter a été laissé in situ dans l artère bronchique respectivement deux jours et six jours Des nécroses étendues sont apparues dans les tumeurs peu de temps après la fin du traitement

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ROENTGEN IRRADIATION AT 200 kV OF NEOPLASMS OF THE NASOPHARYNX

Technique and dose distribution

by

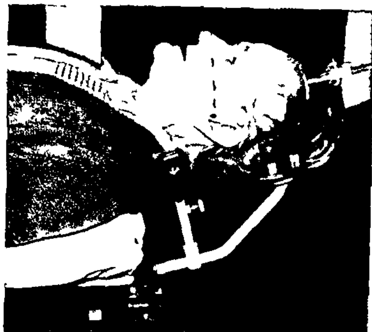
ULLA BRITA NORDBERG and HANS OLIVECRONA

Malignant tumours of the nasopharynx have usually been treated by conventional roentgen therapy. In recent years γ radiation from ^{60}Co sources and high energy roentgen rays from 35 MeV betatrons have also been employed, an attempt was made by SNELLING in 1954 to estimate the dose distribution for some different types of treatment techniques. This paper presents an analysis of the dose distribution in the nasopharynx and adjacent structures obtained by roentgen irradiation at 200 kV with a 4 field technique in the treatment of tumours limited to the nasopharynx.

Technique. A sketch is first made of the contour of the face at the level of the nasopharynx and a lateral roentgenogram is obtained of the skull. The enlargement of the roentgenogram in the sagittal plane can be determined by means of a measuring stick fixed on the forehead and nose of the patient. The true depth of the nasopharynx and the site of the tumour are established and transferred to the previously drawn sketch.

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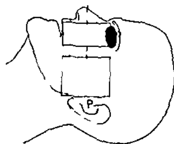


Fig. 1. *Left*: Patient in treatment position. Central plane of irradiated volume and projection of intersection point are marked on the skin. *Above*: Schematic drawing of ports of entrance. Black area represents eyeshield. P = projection of intersection point.

The treatment is planned from four ports, with the beam directed to the same point situated behind the tumour region, with one lateral and one medial field symmetrically on each side (see Fig. 5, point 0). Each field is about 6 × 7 cm at the point of central axis intersection, corresponding to a field of about 5 × 6 cm at the skin. The HVL of the roentgen radiation is 1 mm Cu and the focus axis distance 60 cm. The axis and the beam directions are determined individually to give an optimal dose distribution.

The arrangements for treatment are quite simple and easily reproducible. The patient is placed in the supine position, the head being fixed in a head and neck support (Fig. 1), and a Siemens arc therapy apparatus with light indicated diaphragm is employed. The head of the patient is fixed in such a position that the central plane of the volume to be treated is vertical and directed slightly upwards against the base of the skull (Fig. 1). The point of intersection (see Fig. 5, point 0) is projected onto the skin at each side of the head (Fig. 1, point P, Fig. 5, points P and Q) perpendicularly to the sagittal plane, and the focus skin distance is checked. Treatment of all four fields is then given in one session simply by successively positioning the apparatus at the predetermined angles. It takes about 30 minutes daily to make the arrangements and to give a tumour dose of about 225 rad, which corresponds to a skin dose at each port of entrance of about 150 rad.

The eyes are protected by 3 mm thick lead eyeshields that reach about 0.5 cm within the upper part of the medial fields (Fig. 1). To avoid the

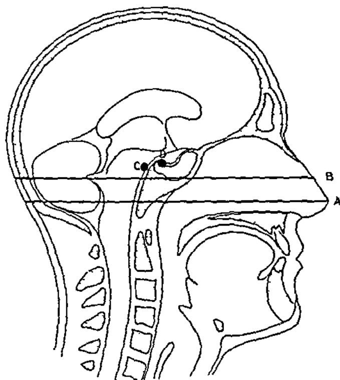


Fig 2 Sagittal section of phantom used for measurements A and B represent planes where the dose distribution has been measured C and D represent the measurement points at the base of the skull

possibility of the shield causing a decrease of the dose to the base of the skull the central plane of the volume to be irradiated is, as mentioned directed slightly upwards

The calculated dose is checked three to four times during the treatment by inserting small condenser chambers through the inferior part of the nasal cavity on each side into the nasopharynx The dose to the lens is measured under the eyeshields a few times by using the same type of chambers To check the arrangements ordinary roentgenograms can be taken on the same film of each one of the four fields by putting a strip of film around the back of the head For further control that the treatment has been carried out in the way intended a strip of graphical film of low sensitivity can be used during the whole treatment session In this manner the four fields show up on the film strip in an approximately orthogonal projection By supplying the measuring chambers in the nasopharynx with a small lead indicator it is possible to deduce the position of the measuring points in the four roentgenograms

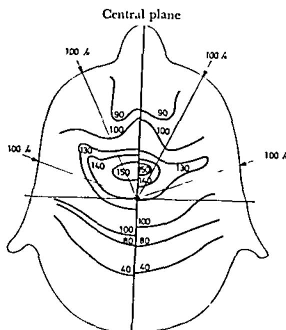


Fig 3 Comparison between calculated (left part of diagram without corrections for bones and air cavities) and measured (right part of diagram in a heterogenous phantom) dose distributions in the central plane A The isodose diagram represents 4 roentgen fields 6 × 7 cm at axis FAD 60 cm HVL 1 mm Cu

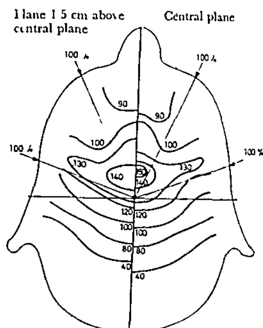


Fig 4 Comparison between the dose distribution in the central plane A and in plane B which is situated 1.5 cm above A (see fig 2) The isodose diagram is from 4 roentgen fields 6 × 7 cm at axis FAD 60 cm HVL 1 mm Cu measurements in a heterogenous phantom

Dose distribution Measurements with small condenser chambers have been made in a heterogeneous phantom of mix D, sculptured on a true cranium The dose distributions in the central plane (A) of the treated region, and in a plane (B) 1.5 cm above this central plane, were determined (Fig 2) In Fig 3, the dose distributions in the central plane are shown, the calculated one to the left and the measured one to the right The calculation was made without correction for bones or for air cavities As may be seen, there is nevertheless a close agreement over the whole treated area between the calculated and measured doses In Fig 4, the results of the measurements in the two different planes A and B from Fig 2 are compared The two dose distributions are substantially the same Measuring chambers have also been placed at the two points C and D (Fig 2) at the base of the skull The dose at these points is the same or slightly lower than that at the site of the nasopharynx in the central plane The dose to C and D is respectively 125 and 135 % of the entrance dose

In Fig 5, to illustrate the results of the measurements clinically the calculated isodose diagram for a patient is shown The figures are normalized to

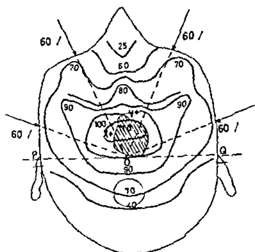


Fig 5 Clinically calculated dose distribution normalized to 100 at site of tumour dose measured on different occasions. O — intersection point of the four beam axes P and Q — project on of point O on the skin on each side of the head hatched area — tumour ring — position of brain stem Point X — 105 104 114 MV 108 Point Y — 97 101 99 100 MV 99

— Isodose diagram from 4 roentgen fields 6 × 7 cm at axis FSD 60 cm HVL 1 mm Cu

100 % at the site of the tumour The dose at point X has been measured three times and that at point Y four times The individual measurements at each point show only a small spread, which indicates a high degree of reproducibility of the treatment The mean values fit well in the calculated isodose diagram The calculated dose distribution in a patient can be checked at only a limited number of points As shown above there is good agreement between calculations and measurements in the total dose distribution in a phantom It thus appears to be justified, from the concordance at two points between the calculated and measured doses to presume clinical validity for the isodose curves calculated without corrections

The dose in the anterior part of the nasal cavity is about 40 % or less of the dose in the nasopharynx The brain stem is situated close to the nasopharynx region and the magnitude of the irradiation to the central nervous system lies between 65 and 85 % of the dose to the tumour region according to the phantom measurements The dose to the lens as measured clinically never exceeds 6 % of the dose to the tumour

Discussion

The nasopharynx has a vertical diameter and a transverse diameter each of about 4 cm and a depth from front to back of about 2 cm it thus occupies a small ellipsoidal space The treatment of lesions limited to this intricate

region therefore demands a technique reliable both in reproducibility and in exactness of beam direction Measurements of the dose in the nasopharynx have been made with the patient lying on an ordinary treatment couch without any reproducible positioning of the head, and with roentgen apparatus for stationary treatment The results of such measurements have been quite unsatisfactory in showing great variations from one treatment to another and generally poor agreement with estimates made from depth dose data It has been impossible to determine whether these differences were real, it was evident, however, that this mode of treatment was not reproducible

By pulling the medial fields away from each other, the reaction of the mucous membrane and the skin of the nose is very slight and causes no discomfort to the patient The beam direction used for the lateral fields ensures that the inner ear receives only a relatively small dose and the dose to the lens is quite tolerable The procedure now described represents a technique which is reliable in reproduction, easy to perform, and based on accurate knowledge concerning the dose to the tumour region and its adjacent structures

SUMMARY

A technique employing an arc therapy apparatus for the treatment of malignant neoplasms of the nasopharynx is described Close agreement has been obtained between the calculated and the true dose distributions as measured both in a phantom and clinically

ZUSAMMENFASSUNG

Eine Bestrahlungsmethode fur maligne Tumoren des Nasopharynx die auf Benutzung eines Pendelgerats beruht wird beschrieben Man konnte eine gute Übereinstimmung zwischen der errechneten und wirklichen Strahlendosis sowohl am Phantom als auch bei der klinischen Anwendung feststellen

RÉSUMÉ

Description d une technique de traitement de tumeurs malignes du nasopharynx au moyen d un appareil de thérapie pendulaire Les mesures sur fantome et sur malade ont montré une bonne concordance entre les distributions de dose calculées et réelles

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FROM THE SECTION OF MEDICINE (DR H VETTER) OF THE DEPARTMENT OF RESEARCH AND ISOTOPES (DIRECTOR DR H SELIGMAN) OF THE INTERNATIONAL ATOMIC ENERGY AGENCY, VIENNA I, AUSTRIA

THE ORGANIZATION OF CLINICAL DOSIMETRY II

Some special topics in treatment planning

by

MONTAGUE COHEN

In part I of this review the four stages of clinical dosimetry — topography, planning treatment and reconsideration — were described in relation to teletherapy In the course of the discussion a number of topics concerned with treatment planning were mentioned but were *not described* In the present paper these topics — transverse tomography, pre calculated treatment plans, atlases of isodose charts and the rapid assessment of treatment plans — will be discussed in more detail Firstly however the general consideration of the four stages of clinical dosimetry will be concluded by applying the same principles to surface interstitial and intracavitary therapy using sealed sources (These forms of therapy are sometimes collectively known as brachytherapy)

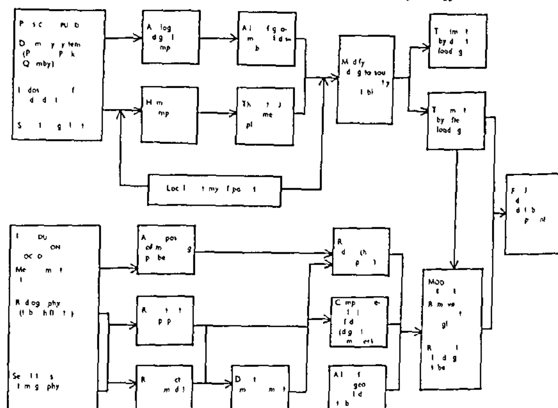
Dosimetry in brachytherapy

The organization of clinical dosimetry in surface interstitial and intracavitary therapy is shown in block form in Table I The general plan is the

Based on a paper read at a Symposium Colloqui sui Rapporti tra Fysica e Medicina Levico-Roncegno Italy 14—20 September 1964 Submitted for publication 16 July 1965

Table 1

Treatment planning in interstitial and intracavitary therapy



same as in teletherapy physical data must be combined with information on the local anatomy of the patient and his disease to produce a theoretical treatment plan which is in turn corrected according to the individual conditions prevailing when the actual treatment is carried out There are, however, important differences in emphasis which arise from the fact that brachytherapy is usually applied to tumours of limited volume in fairly accessible sites Correction procedures depending on, for example, the thickness of lung tissue traversed by a beam of radiation are therefore unnecessary On the other hand, the re assessment of the dose on the basis of the actual treatment, as distinct from the planned treatment, is perhaps even more important than in teletherapy, and is certainly more widely practised It is easy enough to plan an implant or gynaecological application according to a strict geometrical pattern, but it is not so easy to carry out the plan in a living patient Dosage control through radiography of the implant is therefore essential (MEREDITH & STEPHENSON 1945, NUTTALL & SPIERS 1946, MEREDITH 1951, LARR 1953) A number of methods whereby implants can be reconstructed, either on

paper or as a model, have been described (KLIGERMAN et coll 1956 MUSSELL 1956 SMITH 1958, DEVOIS et coll 1958, VAETH & MEURK 1963) The use of multisection transverse tomography for visualizing implants is particularly worth mentioning (EGAN & JOHNSON 1960 PIERQUIN & FAYOS 1960, PIERQUIN, CHASSAGNE & CASIOROWSKI 1960)

The physical input data shown on the top left on Table 1 correspond to the isodose curves and output measurements which are a prerequisite of clinical dosimetry in teletherapy As was pointed out in part I of this review, it is the physicist s responsibility to obtain, by direct measurement or otherwise, full data on all sources of radiation used in therapy In the case of the small sealed sources used in brachytherapy an accurate measurement of the activity of each source is usually made by the manufacturer It is advisable however for the user to check the distribution of activity within the source by autoradiography and to check all radium sources for leakage at 6 or 12 monthly intervals The strength of short lived seeds including radon ^{198}Au and ^{90}Y, should also be measured before use, at least on a sampling basis to check the values quoted by the supplier and the same applies to radioisotopes used in wire form (^{182}Ta and ^{192}Ir) which may be supplied as hairpins or alternatively as long wires which have to be cut to length before use

In contrast to teletherapy isodose curves and dosimetry systems in brachytherapy are usually based on calculation rather than measurement, although it is fairly common practice to check the calculated dose rate in situ by means of a scintillation or photoconductive (usually CdS) probe for example placed in the rectum in the case of radium treatment of the cervix uteri Isodose curves for many individual needles and tubes are available through the Radiation data for medical use — scheme (1964) of the International Atomic Energy Agency It must be remembered that nearly all clinical experience with small sealed sources is based on dosimetry in air, i e the effect of tissue absorption and scattering is neglected This is unimportant for nearby points (say up to 2 cm from a source) but the correction becomes appreciable for more distant points and it is precisely at such points that the dose needs to be known if supplementary external irradiation is planned (For correction factors see WOOTTON SHALEK & FLETCHER 1954, BATHO & YOUNG 1964)

It must further be borne in mind that the most commonly used dosimetric system the Paterson Parker system, is based on a dose rate in air of 8 4 R/hour at 1 cm from a point source of 1 mg of radium (filtration 0 5 mm Pt) although the correct value of this constant is now generally considered to be 8 25 R/hour Indeed there is an interesting group of related problems which remains to be resolved in brachytherapy (a) the conversion of Paterson Parker roentgens to rads (SHALEK 1963) (b) the relationship between the stated dose according

to a formalized dosimetric system such as Paterson Parker and the dose assessed by detailed study using a computer, and (c) the relationship between the dose delivered to a given volume of tissue by implanted sources and that delivered to the same volume by external irradiation — an important matter when 'combined' therapy is to be given, as in cancer of the cervix uteri

It is not proposed to discuss Table 1 in detail since most of the procedures included in the table are well known We shall therefore conclude this section on brachytherapy by referring briefly to four developments in this field

1 Recently there has been a considerable interest in, and development of, afterloading techniques By afterloading is meant the insertion into the tissues, or into a body cavity, of empty tubes or containers representing the radioactive sources The actual sources are loaded into the empty tubes later on, under much more favourable conditions of radiation protection Afterloading is not only advantageous from the protection point of view, but is also conducive to accuracy since it is easier to insert, or re insert, inactive containers into the body than active sources (MOWATT & STEVENS 1956, HENSCHKE 1960, BRASFIELD & HENSCHKE 1961, SUIT et coll 1961, WALSTAM 1962, PIERQUIN & CHASSAGNE 1962, RIDINGS 1963, CHASSAGNE, RAYNAL & PIERQUIN 1963, HENSCHKE, HILARIS & MAHAN 1964, 1965)

2 Another recent development is the use of computers in the dosimetry of small sealed sources The analogue computer of KEMP (1950) has been used for many years, but digital computers are now being brought into this field, both for the calculation in advance of treatment arrays and for the assessment of implants which have already been inserted into the patient (SHALEK & STOVALL 1961, STOVALL & SHALEK 1962, LAUGHLIN et coll 1963, MEURK & ADAMS 1963, ADAMS & MEURK 1964 HOLE et coll 1964)

3 The replacement of radium by artificial radioisotope sources is gathering momentum (The use of gold 198 seeds in place of radon for permanent implants is well established) The isotope most favoured as a radium substitute, particularly for gynaecological work, is caesium 137 (HORSLER, JONES & STACEY 1964, HORWITZ et coll 1964) This isotope has a reasonably long half life (30 years) and its gamma ray energy (0 66 MeV) is significantly lower than that of radium, so that shielding problems (both external and within body cavities) are simplified Until recently, caesium sources were considered unsuitable for use within the body since the active material was available only as a soluble salt but this difficulty has now been overcome Another isotope of great promise is tantalum 192 (half life 74 days, effective gamma ray energy 0 34 MeV) which is available in wire form, particularly suitable for afterloading techniques (HENSCHKE 1958, PIERQUIN 1964, 1965, SIMON 1965)

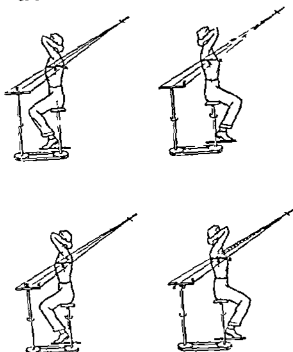


Fig 1 Principle of transverse tomography From STEVENSON (1950) By courtesy of the author and the editors of Brit J Radiol

The use of radium substitutes does not in itself, introduce any fundamental change in the dosimetric procedures and calculations provided that due account is taken of differences in half life specific gamma ray emission constant, oblique filtration and tissue absorption If however the geometry of the sources is greatly different from that of radium needles or tubes — for example if a number of flexible iridium wires are implanted — it may be difficult to utilize the usual dosimetric tables, and another system may be needed, such as the point technique of PIERQUIN & FAYOS (1960)

4 The *International Atomic Energy Agency is currently preparing an* Atlas of dose distributions for brachytherapy, which will include both geometrically perfect arrays of sources and illustrations of the effect of errors and variations in the geometry It is hoped to be able to publish this atlas in 1966 or 1967

Transverse tomography

Transverse axial tomography has been mentioned several times in this review in connection with planning the treatment, assessing the effect of body



Fig. 2. Apparatus for axial transverse tomography with *patient in horizontal position*. *Courtesy Dr. S.* TAKAHASHI and Toshiba Nucleonics Co., Tokyo.

composition and reconstruction of an implant. The method was developed largely in Italy and in France, whereas in the Anglo Saxon countries the technique has, on the whole, been neglected, at least until quite recently. This is in spite of the fact that the theory was first expounded in an American journal (KIEFFER 1938) and one of the earliest papers was in the British Journal of Radiology (STEVENSON 1960) from which Fig. 1 is taken. This diagram shows the working principle: when the film and the patient are simultaneously rotated, in the same direction about parallel axes, only points lying in a single plane of the body, less than 1 mm thick, remain stationary on the film and therefore in focus. All other points are blurred out.

The literature on this subject is abundant and only a few of the papers will be mentioned: VALLEBONA 1948, 1950, FRAIN & LACROIX 1948, FRAIN

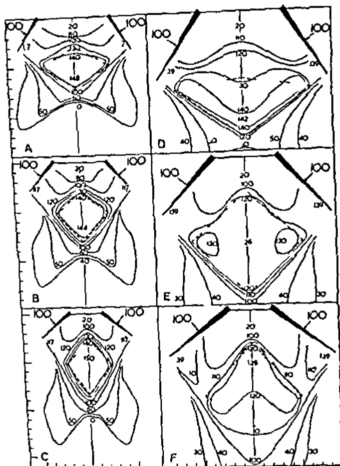


Fig 3 Precalculated wedge field isodose charts From COHEN BURNS & SEAR (1960 b)

et coll 1955 ROSWIT et coll 1959 PIERQUIN 1961 OLIVA 1963 FARR 1964 Papers on the use of transverse tomography for the reconstruction of implants have already been mentioned

The disadvantage of transverse tomography as shown in Fig 1 and described in the papers so far quoted is that the roentgenograms must be obtained with the patient in the vertical position whereas radiotherapy is usually given with the patient lying down This introduces the possibility of a change in the shape of the body and in the relative positions of internal structures as mentioned in part 1 of this paper In order to overcome this difficulty TAKAHASHI & MATSUDA (1960) devised a new form of tomograph which they called

Table 2

Example of dosage table for 8 cm wedge to be used in conjunction with pre-calculated treatment plans — From Cohen, Burns and Sear (1960b)

θ	s (cm)	Plateau dimension (cm)		Mean tumour dose (per cent)	
		Max width	Depth below base line	4 cm field length	16 cm field length
	4 0		5 —11 2	158	161
	6 0		6 —11 9	144	149
70	8 0	14	7 —12 6	132	137
	10 0		8 —13 3	121	126
	12 0		8 —14 0	110	116
	2 0		3 —11 2	158	161
	4 0		4 —12 1	144	148
80	6 0	13	5 —12 9	131	136
	8 0		5 —13 8	119	125
	10 0		6 —14 6	108	114
	2 0		1 7—11 9	143	147
	4 0		2 7—12 9	129	134
90	6 0	12	3 7—13 9	116	122
	8 0		4 7—14 9	105	111
	10 0		5 7—15 9	94	101
	2 0		1 9—12 6	132	137
	4 0		3 1—13 8	118	124
100	6 0	11	4 3—15 0	105	112
	8 0		5 5—16 2	94	101
	10 0		6 7—17 4	84	91
	1 0		1 4—10	139	144
	3 0		2 8—11	123	128
110	4 0	10	3 6—12	115	121
	5 0		4 3—13	108	114
	7 0		5 7—14	95	102
	Hot spot (per cent)			139	135

the 'universal rotatograph' TAKAHASHI has since improved the apparatus so that it can be used either for fluoroscopy or for radiography, and the latest commercial version (Toshiba Nucleonics Co Ltd, Tokyo, Japan) is shown in Fig 2 (See also TAKAHASHI 1965)

Pre-calculated treatment plans

It is sometimes said when a pre calculated treatment plan is used, that the patient is made to fit the plan instead of adapting the plan to fit the patient This is fortunately only a half truth since the rationale of the pre calculated

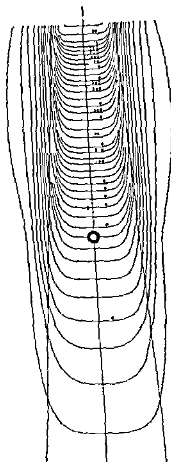


Fig 4

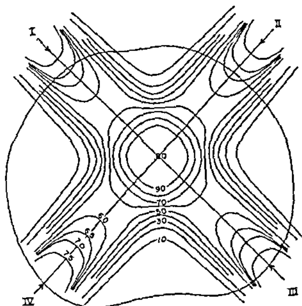


Fig 5

Fig 4 Single field isodose curve based on 100 at a depth in tissue (Co SCD 75 10 × 10) From Du Sault (1959) By courtesy of the author and the editors of Radiology

Fig 5 Four field isodose charts (Co fields 6 × 6 at right angles) with contour of patient added From Du Sault (1959) By courtesy of the author and the editors of Radiology

plan is that it should be independent of the contours of individual patients or at least readily adaptable to any patient Nevertheless it must be stated that a single pre calculated plan is unlikely to be applicable to all patients and tumours and the method is useful only if a series of such plans is available to cover a broad range of conditions

One of the best examples of the method is for two oblique wedge fields *This technique was first used by* Ellis & Miller *(1944) for 200 kV roentgen* rays and was further developed by Ellis et coll (1950) The method was systematized by Cohen (1959) who analysed the effect of the different para meters of the system A similar analysis was carried out by Cohen Burns &

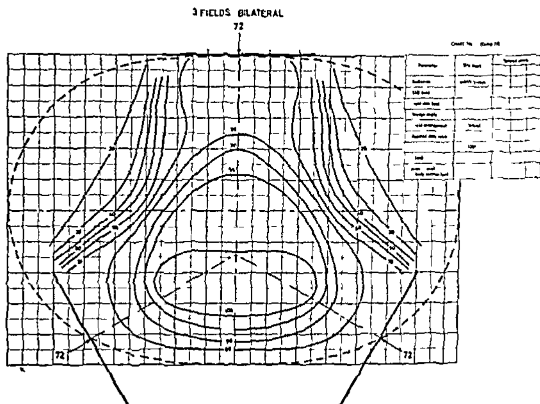


Fig 6 Sample page from Atlas of multiple field isodose charts From COHEN (1966) By courtesy of IAEA Vienna

SLAR (1960), for wedge filters used with cobalt 60 radiation, and Fig 3 shows some examples of isodose charts taken from this paper The complete set of charts is, of course, much larger, and the charts have to be used in conjunction with tables such as that illustrated in Table 2

The purpose of the wedge method is to treat tumours located near the surface of the body but extending to some depth below the surface by means of 2 fields on one side of the body only Thus the size of the individual patient does not matter, and the only aspect of the patient which comes into the picture is the necessity of fitting the curved entrance surface of the patient into the space defined by the two oblique fields In the case of 250 kV roentgen rays this problem is solved by irradiating through a wax block which fills the space between the applicator end and the patient s skin For high energy radiation, however, it is desirable to use a compensating filter The difference between these techniques was illustrated in Fig 3 of part I

Wedge filters are now very widely used in radiotherapy especially with high energy radiation, and an extensive literature exists Only those papers will be mentioned here which have made an important contribution not

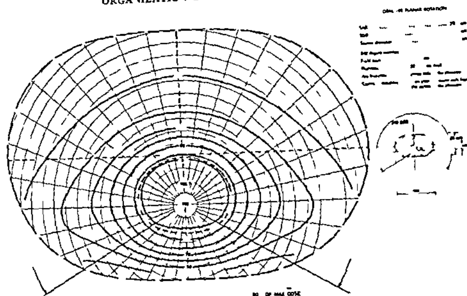


Fig 7 Sample page from Atlas of moving field isodose charts From TSIEN CUNNINGHAM & WRIGHT (1966) By courtesy of IAEA Vienna

merely to the design and construction of the filters but to the concept of pre calculated plans MICELI BONO & RIMONDI 1964 (^{137}Cs) CAVINA et coll 1962 (^{60}Co) STEWART 1960 (4 MV roentgen rays) VAN ROOSENBEEK & GRIMM 1961 (22 MV roentgen rays) SEAR 1959 (general analysis)

Another important type of pre calculated plan is derived from the method of BRAESTRUP & MOONEY (1955) which was further developed by DU SAULT (1959) The basis of the method is the single field isodose curve referred to 100 % at a depth in tissue instead of at a point at or near the surface The isodose curves are supposed to extend indefinitely both above and below the reference point (Fig 4) When a number of such fields converge at the reference point a multiple field isodose chart is obtained which is independent of the contour of the individual patient This contour may in fact be drawn on the chart and the dose which has to be applied to each field to ensure equal contributions at the centre point may be calculated (Fig 5) In these circum stances the dose distribution in the centre of the chart is exactly reproduced, and errors are incurred only near the surface where in general the dose is not critical The method has been further extended and improved by MACDONALD (1961) PFALZNER (1962) GIAUX et coll (1964) and LEGARE (1964)

Many other examples of pre calculated plans could be given for example for tangential irradiation of the breast and for parametrial irradiation by

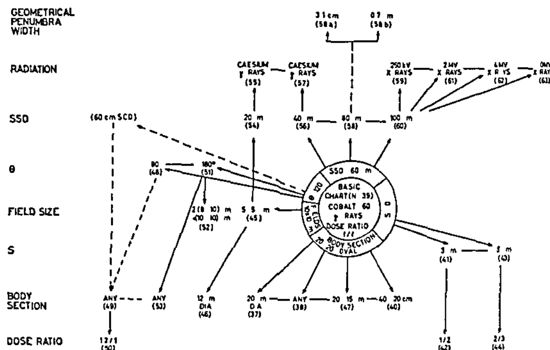


Fig 8 Radial arrangement of 3 field charts in group IV of the Atlas of multiple field isodose charts From COHEN (1966) By courtesy of IAEA Vienna

means of opposed fields following intracavitary radium treatment The essential feature of the method is that only one or two parameters of the individual patient are relevant so that a set of plans covering all sizes of patients can be prepared and systematized

Atlases of isodose charts

An atlas of isodose charts is, superficially, similar to a set of pre calculated plans but in fact differs from such plans in that the charts in an atlas are not confined to situations which are independent of the individual patient In a sense, every radiotherapy department builds up its own atlas over a period of time, but these collections (which of course derive from treatment plans produced for actual patients) differ from a true atlas in that they lack the two essential elements of systematization and analysis Indeed, to turn a collection into an atlas is a formidable task, as the author and his colleagues in the International Atomic Energy Agency discovered when they decided to prepare such atlases for high energy radiation (including cobalt and cesium gamma rays)

These atlases are for multiple fields (COHEN 1965) and moving beams (TSIEN, CUNNINGHAM & WRIGHT 1966), sample pages are shown in Figs 6

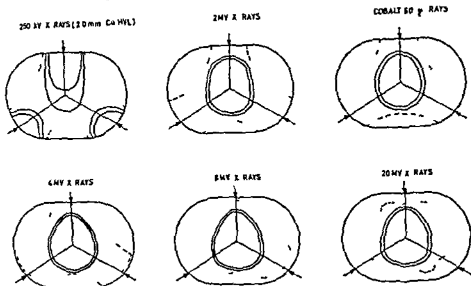


Fig 9 Plateau diagrams for 3 field irradiation with different beam energies (10 × 10 cm fields 100 cm SSD) The lines represent 90 80 and 50 isodoses where 100 is the maximum in the target region (See also fig 11) From COHEN (1966) By courtesy of IAEA Vienna

and 7 respectively (A third atlas for single fields has also been prepared WEBSTER & TSIEN 1965) Space does not permit a detailed discussion of these atlases and their use but one or two important features of the multiple field atlas will be mentioned Classification is based on the number of fields and their arrangement for example 2 opposed fields 3 field bilateral irradiation, and so on Within each main section there is a basic plan with average or typical values of all parameters and the other charts in the section are linked to this chart on an approximately radial basis as illustrated in Fig 8 Each isodose chart is related to at least one other chart, and often to several other charts by a change in one parameter only The body contours are necessarily idealized and for this purpose the oval outline proposed by HAYNES & FROESE (1957) has been adopted In this atlas and in the moving beam atlas the isodose charts are supplemented by a detailed analysis of the effect of the various parameters on the dose distribution This analysis takes the form both of graphs and of so called plateau diagrams, which are abbreviated and simplified isodose charts produced by the method to be described below An example of a group of six of these diagrams for three fields converging at the centre of an oval of axial dimensions 30 × 20 cm (10 × 10 cm fields 100 cm SSD) for various beam energies is shown in Fig 9 Such groups of plateau

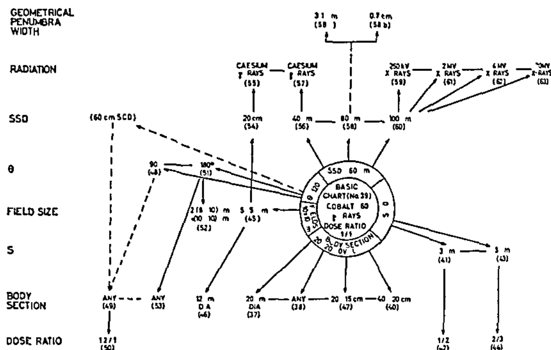


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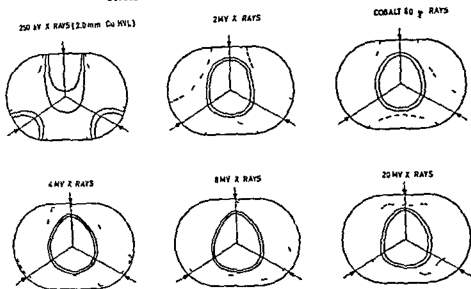


Fig 9 Plateau diagrams for 3-field irradiation with different beam energies (10 × 10 cm fields 100 cm SSD) The lines represent 90 80 and 0 isodoses where 100 is the maximum in the target region (See also fig 11) From COHEN (1966) By courtesy of IAEA Vienna

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diagrams provide an effective means of illustrating the effect of a given parameter A detailed graphical analysis is also given in the moving beam atlas

While the IAEA atlases are the most comprehensive of their type yet published, mention should also be made of the important sets of dose distributions for moving beam therapy published by DAHL & VIKTERLOF (1958) (250 kV roentgen rays) and by HULTBERG et coll (1959) (cobalt 60 radiation)

Rapid assessment of treatment plans

As was pointed out in part I of this paper, it is difficult for a human computer to produce isodose charts for individual patients quickly enough to enable the final treatment plan to be chosen from a number of alternative charts The author has therefore devised a method whereby this choice can be made on the basis of data which are intermediate between a full isodose chart and the dose at one or two points only At present, the method has been fully worked out only for symmetrical field arrangements but it is being extended to asymmetrical arrangements The following is intended only as a summary, since a detailed description of the method will be published elsewhere Two operations are involved

1 The combined dose distribution is plotted along the axis of symmetry This is rapidly done, without combining isodose curves, by drawing a line at the appropriate position on the single field isodose chart From the axial distribution curve may be read off (i) the maximum percentage depth dose, which is called 100 %, and (ii) the positions of the 90 %, 80 % and 50 % dose levels

2 The edges of the various beams are drawn on the outline representing the patient Except for very short SSD's, beam divergence may be ignored The area in which all the beams overlap represents the area enclosed by the 80 % isodose curve, except that this area may be extended into certain areas in which some, but not all of the beams overlap (e g 2 out of 3 beams, or 3 out of 4) Simple rules may be propounded for these extensions The envelope of the beam edges (excluding the exit positions of each beam) represents the 50 % isodose curve, except in certain cases (for which, again, there is a simple rule) for which this envelope represents instead the 40 % or the 30 % curve (Fig 10)

3 Combining (1) and (2), it is possible to sketch an abbreviated isodose chart (plateau diagram) which shows only the 90 %, 80 % and 50 % isodose curves Such a diagram contains in fact all the information needed to assess the suitability of a treatment since it shows the position, size and shape of the region of uniformity (as depicted by the 90 % line), the rapidity of the fall off

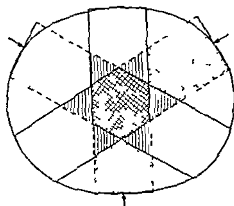


Fig 10 Method of rapid assessment of multiple field distributions by considering area of beam overlap

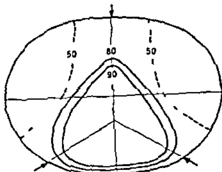


Fig 11 Abbreviated isodose chart (plateau diagram) of field arrangement shown in fig 6 The 100 point (maximum in target region) not shown

outside this region (as shown by the relationship between the 90 % and 80 % lines) and finally some information about the dose outside the tumour region (as represented by the 50 % line) In Fig 11 the plateau diagram for a 3 field arrangement is shown and this may be compared with the full isodose chart for the same field arrangement shown in Fig 6

However even if a full isodose chart is available, it is doubtful if we make use of much more information than this in assessing the value of the chart in fact a full isodose chart contains so much data that we are bound to extract the salient features before it can be comprehended All that the proposed method does is to examine the nature of the extracted data and to produce this information but no more by a short cut

Conclusions

Clinical dosimetry today is in a most interesting stage of development A few years ago the main pre occupation in radiotherapy was the switch over to high energy radiation This process is of course continuing but the centre of interest has moved towards more exact dosimetry with high energy units whose existence is taken for granted Two problems must now be solved not simply in a few large and advanced radiotherapy centres but in centres all over the world firstly how can we ensure that an optimum treatment plan is prepared for each patient in accordance with the individual characteristics of the patient and his tumour and secondly how can we take into account,

on a routine basis, the obvious fact that a patient is not exactly the same as a rectangular tank of water

It is fashionable nowadays to hail the digital computer as the answer to all dosimetric problems The role of the computer in clinical dosimetry is by no means agreed, and it would be unwise to regard the computer as a universal panacea On the one hand it is argued that the computer will enable an individual treatment plan to be tailored to the needs of each patient But it is also said (e g SHALEK 1963) that this is not the ideal role for the computer instead, computers should be used to produce a large number of treatment plans, of the pre calculated type, as well as bigger and better atlases of isodose charts and analyses of the effect of each parameter In the present author's opinion there will be need, and scope, for several types of application and, indeed, it is unrealistic to take a narrow view as to the application of computers

At this point, a word of caution as to pre calculated plans is perhaps neces sary There is no doubt that the judicious use of such plans is a god send in a busy radiotherapy department If half the patients are treated through pre calculated plans, then the other half, for whom such plans are inapplicable, will have a better chance of the individual calculations which their conditions demand

Now it is easy to conclude from this that the more pre calculated plans a department has available the more patients can be treated by this method and the better the choice for the individual This is true up to a certain point but beyond that the system can become self defeating Suppose, for example, one has 10, or even 20, isodose charts of pairs of wedge fields These can be spread out side by side on the table and the choice for a given patient made by direct comparison But if one has 200 such charts, a direct comparison is no longer so easy The rapid choice of the correct chart now depends on the use of a system of classification, not, however, classification on the basis of the physical parameters, such as field size and angulation, but on the basis of the size and position of the tumour The more treatment plans are produced, by computers or otherwise, the more urgent becomes the need for an acceptable analysis of the isodose charts themselves, so that a rational comparison of large numbers of charts becomes possible This is the kind of analysis we have tried to undertake in the atlases and in the simplified method of assessing charts that has been described in this paper

Finally, it may be inquired what the policy on treatment planning of a radiotherapy centre with limited resources and trained staff should be, e g a centre with only one physicist and perhaps a technician or two, and whether an optimum division of time and effort is possible between the different stages of clinical dosimetry and between the different types of treatment planning

No universal answer is possible but we may conclude by offering a 5 point plan as a basis for further discussion

1 During the first few months after his appointment and again whenever new equipment is installed the physicist must spend at least half his time on physical dosimetry

2 For the first 2 or 3 years it is necessary to concentrate on water phantom dosimetry Simple corrections should be applied for lung tissue but no attempt should be made to assess these corrections individually During this period the physicist must become thoroughly familiar with treatment planning

3 Right from the start simple corrections for field obliquity should be applied Alternatively compensating filters should be used routinely Similarly, from the start, attention should be given to accuracy during the setting up of the patient and delivery of the dose

4 Routine treatment planning should eventually become the responsibility of either a technician specially trained for this purpose or of junior doctors who are training to be radiotherapists In either case, overall supervision should rest with the senior radiotherapist in association with the physicist It should be the aim of the physicist that after the first 2 or 3 years he should not need to spend more than 10—20 % of his time on routine planning This will depend of course on the proportion of patients for whom pre calculated plans are used This proportion is a matter of individual preference and circumstances but as a rough guide 50 % of patients may be found suitable for this method However before this stage is reached the physicist must produce, or obtain suitable plans

5 Eventually more and more of the physicist s time should be devoted to the final ('reconsideration') stage of clinical dosimetry This may be regarded as research in clinical dosimetry but the aim should be to produce a measurement and correction technique acceptable for routine use

Acknowledgements

The author acknowledges with pleasure his debt to Dr Herbert VETTER for helpful discussion and advice and to Dr Henry SELIGMAN for permission to publish this paper

SUMMARY

The organization of clinical dosimetry in four stages which was described for teletherapy in part I of this review is now discussed with reference to brachytherapy Some recent developments are mentioned including afterloading computer evaluation of doses due to arrays of sealed sources and the replacement of radium by other radioisotopes Some special topics mentioned earlier in this review are described in more detail axial transverse tomography pre-calculated treatment plans atlases of isodose charts and the rapid assessment of treatment plans A policy for treatment planning is suggested for developing radiotherapy centres

ZUSAMMENFASSUNG

Die Einteilung der klinischen Dosimetrie in vier Stufen, wie im Teil I für die Teletherapie beschrieben worden ist, wird jetzt mit Hinsicht auf die Brachytherapie besprochen Neuere Entwicklungen werden angeführt einschliesslich afterloading automatischer Berechnung von Dosen plombierter Bestrahlungsquellen und der Ersatz von Radium durch andere Isotope Einige Spezialfragen, die früher in dieser Übersicht erwähnt wurden, werden im Detail beschrieben axiale transversale Tomographie, vorberechnete Behandlungspläne Atlasse von Isodosenkarten und die rasche Herstellung von Behandlungsplänen Massnahmen für die Therapie Planung in neuen radiotherapeutischen Zentren werden vorgeschlagen

RÉSUMÉ

L organisation de la dosimétrie clinique en quatre phases décrite pour la téléthérapie dans la première partie de cette revue est maintenant appliquée à la brachythérapie L auteur cite certains perfectionnements récents tels que afterloading l utilisation de calculatrice automatique pour évaluer la dose donnée par une série de sources scellées le remplacement du radium par d autres radio isotopes Certains sujets cités précédemment dans ce travail sont décrits de façon plus détaillée la tomographie axiale transverse les plans de traitement précalculés, les atlas de courbes isodoses le choix rapide de plans de traitement L auteur propose comment procédér à l organization des traitements dans les centres de radiothérapie en développement

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REGENERATION OF BONE MARROW CELLS IN RATS FOLLOWING CYCLOPHOSPHAMIDE OR TOTAL BODY IRRADIATION

by

HERMAN HOST

In a previous study (HOST 1966a) differences were disclosed in the recovery pattern of granulocytes in rats, after single doses of cyclophosphamide a nitrogen mustard derivative, and respectively, after total body irradiation *Bone marrow studies were initiated in order to throw light on the underlying* mechanism of the differences observed in the peripheral blood The present paper reports comparative studies on the proliferation rates of the different types of marrow cells after injection of cyclophosphamide and after exposure to total body irradiation Proliferation rates of the marrow cells were studied by a modified colcemid method (HOST 1966b)

Material and Methods Hooded male rats of 200 to 280 g bodyweight, 70 to 94 days old, were used Standard laboratory rations and water were supplied ad libitum

A total of 148 animals were used in the experiments 74 in the cyclophospha mide series and 74 in the irradiated series Each of the two series comprised

From Norsk Hydro s Institute for Cancer Research the Norwegian Radium Hospital Montebello Oslo Norway Submitted for publ cation 23 December 1965

Book reviews

Protection contre les radiations Manuel pratique Par J D Abbat J R A Lakey et D J Mathias 249 pages 3 plates, 44 illustrations and 35 tables Masson et Cie Paris 1963 36 NF

This is a translation of an English book, about which the present reviewer wrote in this journal (Vol 58 p 160 1962) — — — considerable attention is devoted to methods and equipment to prevent exposure of personnel to radiation from radioisotopes while protection against roentgen rays is more briefly treated The organisation and methods of medical control supervision of work and monitoring of personnel and localities are discussed and large parts of the ICRP recommendations are reprinted The subject is treated in a rather elementary way — — — the book may on the whole be recommended as a first introduction A number of nomograms and tables for the approximate calculation of shields etc seem to be of practical value

The translation follows the original rather faithfully but where differences are noted they are seldom improvements However the points where the text is impaired only concern details and in general the above opinion on the English book also applies to the French version

Sven Benner

Sonderausschuss Radioaktivität, Bundesrepublik Deutschland Dritter Bericht bis Mai 1963 131 Seiten 22 Abbildungen und 14 Tabellen Georg Thieme Verlag Stuttgart 1963 Preis 16 80 DM

The present book is the third in a series of reports from the West German Special Committee for Radioactivity The two earlier were briefly reviewed in the May 1959 and April 1960 issues of this journal

The results of German measurements of radioactive contamination of air water soil foodstuffs and human subjects during the period from 1955 to the autumn of 1962 are reported Radiation doses to the population from natural sources contamination of the biosphere and various other sources of radiation are evaluated and the ensuing hazards for various types of radiation injury are discussed The Committee recommends a coordination of current measurement activities pursued by various institutes a systematic public information activity pre planning of protection measures to be taken in case of a significant increase of biospheric contamination and the initiation of research programs on unsolved questions in physics chemistry and radiobiology There is finally a brief introduction to the elements of radiobiology and a short glossary of terms

While much more modest in volume and scope than the U N Radiation Committee reports (to which there are frequent references) the book contains much useful information and should be of considerable interest to those concerned with these matters

Sven Benner

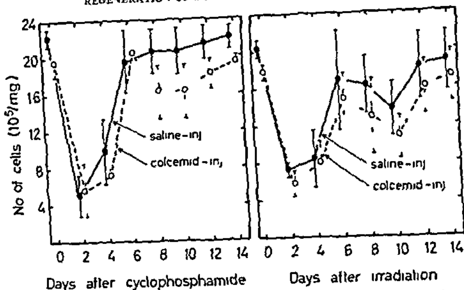


Fig 1 Number of nucleated cells in bone marrow at various times after cyclophosphamide and total body irradiation ●——● saline injected ○ ○ colcemid injected The 95 confidence limits are indicated

rates were estimated (HOST 1966b) Colcemid was injected in doses of 1 mg/kg bodyweight The injections were performed at the same time of the day (between 8 and 9 a m)

Results

The results of the marrow cell counts in the untreated and the sham treated animals were subjected to an analysis of variance to test possible systematic variations with time and the results indicated no consistent trend It therefore seems justified in the following figures and tables to simplify the presentation of these data by depicting them all at zero time

Effects on total nucleated marrow cells Both cyclopho phamide and total body irradiation in the applied doses depressed the number of total nucleated marrow cells to about 25 to 30 per cent of the initial value (Fig 1) Maximum depression occurred on the second day after treatment and was followed by recovery The latter was more rapid and complete in the cyclophosphamide treated animals In the irradiated groups of rats, a slight secondary drop was observed during recovery at about 8 to 10 days after treatment

The general trend was essentially the same for the saline injected and the colcemid injected animals in the latter however, the marrow cell counts remained at a lower level than in the former This is in agreement with

4 untreated, 14 sham treated and 56 treated animals cyclophosphamide injected or irradiated The four untreated animals were sacrificed and examined on day 0 On days 2, 4, 6, 8, 10, 12, and 14 after treatment, two sham treated and eight treated animals were sacrificed and examined Animals were selected at random as regards type of treatment (no treatment, sham treatment, real treatment) and day of sacrifice

The treatment procedures have been described in detail previously (HOST 1966a) Cyclophosphamide (Sendoxan, Pharmacia, Uppsala) was injected into the exposed vena femoralis during ether anesthesia Sham treated animals were injected with physiologic saline Total body roentgen irradiation was carried out at 200 keV (half value layer 1 05 mm Cu) The animals were irradiated individually in a cylindric container Sham treatment was performed by placing the control animals in the container for the same duration as the irradiated animals

Preliminary studies disclosed that 50 mg/kg bodyweight of cyclophosphamide and 350 R total body irradiation produced an almost identical initial depression of the total nucleated marrow cells These doses were therefore used in the comparative studies

Total nucleated marrow cells were counted and estimated in number per mg bone marrow (HOST 1966 b)

Smears for differential counts were taken from the middle part of the femur by the brush method (BURKE, BROTHERSTONE & HARRIS 1955) and stained by May Grunewald and Giemsa The smears were interpreted without knowledge of previous treatment Differential counts were done on one thousand cells and the absolute number of each cell type was expressed per mg of bone marrow Classification of cell types and stages of mitosis was performed as previously described (HOST 1966 b) The number of cells in prophase and metaphase per 1 000 cells capable of division was estimated on the basis of counts of 500 cells in each cell line About 90 to 95 per cent of the mitotic cells were classified as either myeloid or erythroid The others were difficult to place, they were possibly reticular or lymphocyte like cells in mitosis and were not included in the study on proliferation rates and cell renewal

The measurements of proliferation rates were made as follows At successive time intervals after treatment (irradiation or cyclophosphamide) equal numbers of animals, selected at random, were injected subcutaneously with colcemid (Ciba, Basel) or physiologic saline The rats were sacrificed 2 1/2 hours later, and marrow samples for total counts, differential counts and mitotic counts were taken The numbers of mitoses arrested by colcemid were compared with those in animals injected with physiologic saline, and proliferation

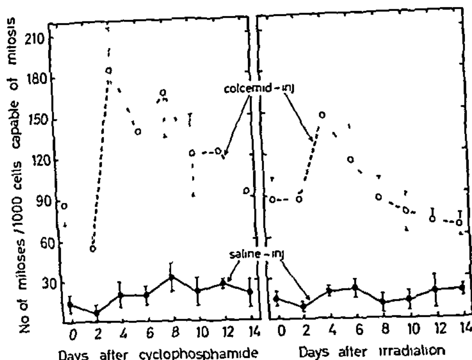


Fig 4 Mitotic index of myeloid cells at various times after cyclophosphamide and total body irradiation ●———● saline injected ○ ○ colcemid injected The 95 confidence limits are indicated

previous findings (Host 1966b) which indicated that colcemid reduces the number of total nucleated marrow cells

Effects on myeloid cells The pattern of changes in the number of dividing myeloid marrow cells after treatment with the two agents is given in Fig 2 On the second day the counts were reduced to about one third of the initial value recovery then occurred in the course of two days In the cyclophospha mide treated animals the number remained at the upper limit of the normal range during the following 4 to 5 days, whereas in the irradiated animals the number stayed in the lower range for a similar period of time

The initial depletion of the non dividing myeloid cells ran almost parallelly in the cyclopho phamide injected and the irradiated animals (Fig 3) Mini mum values about one third of the pre treatment values were registered on the 4th day or two days later than in their precursor cells Recovery was evident in all the treatment groups in the course of days 6 to 8 In the cyclo

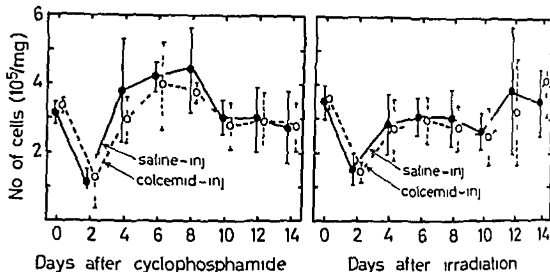


Fig 2 Number of dividing myeloid cells in bone marrow at various times after cyclophosphamide and total body irradiation ●———● *saline injected* ○ ○ colcemid injected The 95 % confidence limits are indicated

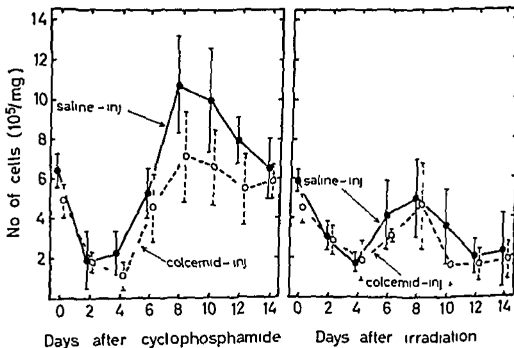


Fig 3 Number of non dividing myeloid cells in bone marrow at various times after cyclophosphamide and total body irradiation ●———● saline injected ○ ○ colcemid injected The 95 % confidence limits are indicated

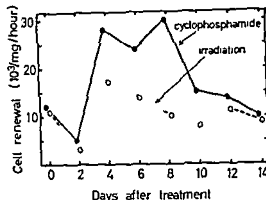


Fig 5 Myeloid cell renewal per mg of bone marrow per hour at various times after cyclophosphamide (●——●) and total body irradiation (O O)

The number of arrested mitoses in the latter remained at a level significantly above normal for a longer time period as compared to the irradiated animals in which counts significantly above normal were observed only on the 4th day after exposure These findings suggest a higher mitotic activity during recovery in the cyclophosphamide treated animals

The data in Table 1 indicate that the mitotic time of the myeloid cells which was calculated from the formula given by ALLEN SMITH & GARDNER (1937) after both types of treatment was reduced during the initial phase of regeneration Later on however the mitotic time increased to levels above the pre treatment ones especially in the irradiated animals

The calculated mitotic rate of the myeloid cells (Table 1) was reduced on the 2nd day while in the irradiated animals it remained within the normal range An explanation of this may be that the recovery of the myeloid cells possibly started earlier in the irradiated than in the cyclophosphamide injected animals However the speed of myeloid regeneration seemed to be faster in the last mentioned group Thus, in the cyclophosphamide injected animals the mitotic rate increased during recovery to levels above normal on the 4th day and remained at this level for about a week On the other hand the mitotic rate of the myeloid cells in the irradiated animals exceeded the pre treatment values only from the 4th to the 6th day

The data on absolute myeloid cell renewal illustrated in Fig 5, emphasize more clearly the large difference in cell production during recovery between irradiated and cyclophosphamide treated rats The absolute myeloid cell renewal represents the product of the mitotic rate and the number of dividing myeloid cells per mg bone marrow As appears from Fig 5 the myeloid cell renewal was more than twice the normal during the 4th to the 8th day in the

Table 1

Mitotic time and mitotic rate in marrow cells at various times after cyclophosphamide (50 mg/kg) and total body irradiation (350 R)

Days after treatment	Myeloid cells				Erythroid cells			
	Cyclophosphamide		Irradiation		Cyclophosphamide		Irradiation	
	Mitotic time in hours	Mitotic rate*	Mitotic time in hours	Mitotic rate*	Mitotic time in hours	Mitotic rate*	Mitotic time in hours	Mitotic rate*
0	0 41	34	0 44	33	0 48	50	0 49	61
2	0 27	22	0 26	35	0 11	43	0 25	76
4	0 26	73	0 32	59	0 27	78	0 44	91
6	0 34	56	0 49	45	0 45	69	0 50	94
8	0 46	67	0 32	33	0 30	67	0 45	87
10	0 45	49	0 42	31	0 46	62	0 50	76
12	0 59	46	0 68	28	0 50	62	0 65	65
14	0 54	36	0 81	26	0 34	91	0 52	73

* Average number of cells which complete their mitosis per hour per 1 000 cells capable of cell division

phosphamide-saline injected animals, values significantly above normal were observed on days 8 to 12 In the irradiated animals, on the other hand, the initial recovery of the non dividing myeloid cells was followed by a second drop which was most accentuated at about the 12th day

The patterns of myeloid cell response to the two different treatments agree well with previous observations Thus temporary normalization of the myeloid marrow cell population has been described during recovery after total body irradiation both in guinea pigs (HARRIS 1956, 1959) and in rats (HULSE 1961) Likewise, an overshooting production of myeloid cells has been found after treatment with nitrogen mustard derivatives (ELSON, GALTON & TILL 1958, PLIESS & FASSBENDER 1961, BIERBRAUER 1961)

Proliferation rates of myeloid cells As demonstrated in Fig 4, the mitotic index, i e the number of mitoses per 1 000 cells capable of mitosis, was slightly below the pre treatment values two days after cyclophosphamide as well as after irradiation During the following days, the mitotic index in the irradiated animals rose to about normal levels and in the cyclophosphamide treated animals to levels in the upper range of normal Concurrently, the changes in the number of mitoses arrested during the action of colcemid were more marked, especially in the cyclophosphamide treated animals (Fig 4)

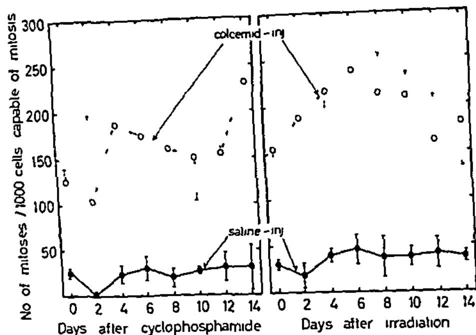


Fig 8 Mitotic index of erythroid bone marrow cells at various times after cyclophosphamide and total body irrad ation ●———● sal ne njected ○ ○ colcemid injected The 95 confidence limits are nd cated

cyclophosphamide treated animals while in the irradiated animals the cell renewal was only slightly increased

Effects on erythroid cells The data presented in Figs 6 and 7 indicate that the erythroid precursor cells were very sensitive to radiation as well as to cyclo phosphamide On the 2nd day the number of dividing erythroid cells was lower in the cyclophosphamide treated than in the irradiated animals (Fig 6), while the number of non dividing erythroid cells (Fig 7) was about the same in the two treatment groups The dividing erythroid cells thus seemed to be more sensitive to cyclophosphamide than the non dividing cells As far as the data go they seem to indicate a similar response pattern in the irradiated groups

Recovery was evident on the 4th day and normal values were regained two days later A secondary drop most marked in the cyclophosphamide in jected animals was observed on days 8 to 10 The recovery pattern was nearly the same both in the dividing and in the non dividing erythroid precursors

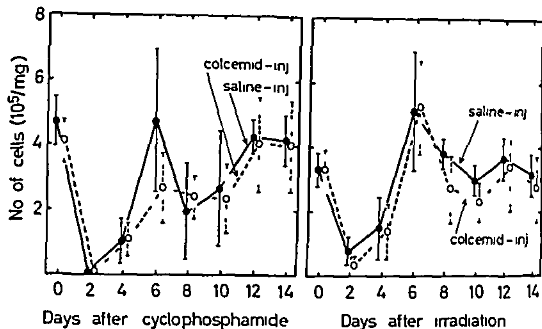


Fig 6 Number of dividing erythroid cells in bone marrow at various times after cyclophosphamide and total body irradiation ●———● saline injected ○ ○ colcemid injected The 95 % confidence limits are indicated

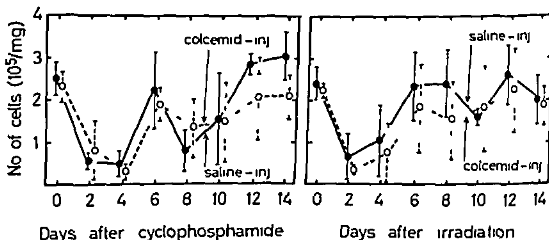


Fig 7 Number of non dividing erythroid cells in bone marrow at various times after cyclophosphamide and total body irradiation ●———● saline injected ○ ○ colcemid injected The 95 % confidence limits are indicated

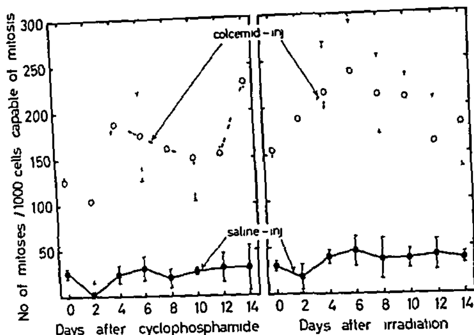


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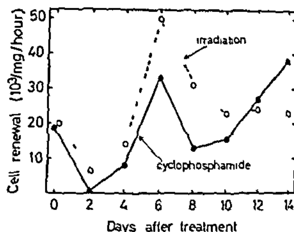


Fig 9 Erythroid cell renewal per mg of bone marrow per hour at various times after cyclophosphamide (●——●) and total body irradiation (○ ○)

after the two types of treatment This is in contrast to the mode of myeloid cell regeneration after irradiation and after cyclophosphamide, where the two treatments led to different recovery patterns

Late, acidophilic, normoblasts occurred frequently in the bone marrow in both series on the 2nd day, on which these cells comprised the major part of the non dividing erythroid cells Acidophilic normoblasts are seldom observed in the bone marrow of rats, under normal conditions, as the cytoplasma of erythroid precursors in this species retains an element of basophilia much later than the corresponding cells in man (HULSE 1964) Occurrence of late, acidophilic, normoblasts has previously been reported by LAMERTON, BELCHER & HARRISS (1956) after irradiation of rats with non lethal doses They suggested that irradiation produced a hold-up in the release of the mature cells from the marrow

Proliferation rates of erythroid cells On the 2nd day, both the mitotic index and the number of mitoses arrested during the action of colcemid (Fig 8) were lower in the cyclophosphamide treated than in the irradiated animals Ionizing irradiation thus had a less depressive effect on erythropoiesis than had cyclophosphamide Furthermore, the regeneration started earlier after irradiation than after cyclophosphamide

The data on cell renewal in Fig 9 indicate a higher erythroid cell renewal in the irradiated than in the cyclophosphamide treated animals during the initial phase of regeneration, in contradistinction to the findings on the myeloid cell renewal (cf Fig 5) A temporary overshoot in erythropoiesis occurred during recovery in both the irradiated and the cyclophosphamide-treated animals

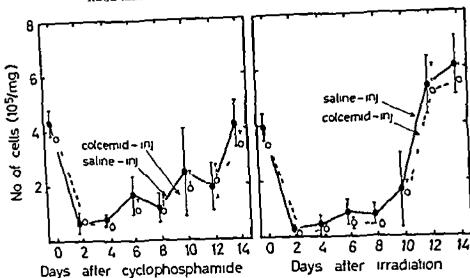


Fig 10 Number of lymphocyte like cells in bone marrow at various times after cyclophosphamide and total body irradiation ●———● saline injected ○ ○ colcemid injected The 95 confidence limits are indicated

The mitotic time of the erythroid cells (see Table 1) was reduced during early recovery and followed a pattern similar to that observed in the myeloid cells

Effects on lymphocyte like cells The depletion phase and the initial recovery period of the lymphocyte like cells occurred almost parallelly in the different groups (Fig 10) These cells were very sensitive to treatment the number on the 2nd day being only 10 to 15 per cent of the normal Differences were observed in the recovery pattern from the 10th day, and onwards The lympho cyte like cells in the cyclophosphamide treated animals rose only to sub normal or normal values these being regained later than normalization of myelopoiesis and erythropoiesis (Figs 3, 6 and 7) In the irradiated animals, on the other hand the lymphocyte like cells rose to levels considerably above normal This increase in the number of such cells in the irradiated animals occurred con currently with the second drop in number of the myeloid cells (cf Fig 3) but after the recovery of the erythroid cells (cf Figs 6 and 7)

The occurrence of large numbers of bone marrow cells resembling lympho cytes has been reported in various species during recovery after total body irradiation (DENSTAD 1943 BRECHER ENDICOTT, GUMP & BRAWNER 1948 HARRIS 1956 YOFFEY 1960) The significance of this finding has been subject

Table 2

'Reticulum cells, plasma cells and 'damaged' cells in bone marrow at various times after cyclophosphamide (50 mg/kg) or total body irradiation (350 R) — The values represent the mean of 4 animals with 95 % confidence limits

	Cyclophosphamide			Total body irradiation		
Days after treatment	Reticulum cells 10^3 cells/mg	Plasma cells 10^3 cells/mg	Damaged cells 10^3 cells/mg	Reticulum cells 10^3 cells/mg	Plasma cells 10^3 cells/mg	Damaged cells 10^3 cells/mg
0	98 ± 41	9 ± 6	26 ± 6	77 ± 16	5 ± 3	32 ± 10
2	74 ± 48	14 ± 6	11 ± 6	74 ± 19	14 ± 6	19 ± 6
4	118 ± 76	17 ± 16	9 ± 3	61 ± 26	10 ± 3	17 ± 3
6	97 ± 29	7 ± 3	34 ± 10	84 ± 41	6 ± 6	34 ± 29
8	108 ± 70	6 ± 3	16 ± 10	78 ± 13	5 ± 3	32 ± 13
10	71 ± 22	16 ± 12	22 ± 10	84 ± 26	6 ± 3	33 ± 10
12	92 ± 62	21 ± 13	26 ± 10	111 ± 35	7 ± 6	35 ± 3
14	93 ± 41	15 ± 10	14 ± 10	88 ± 32	6 ± 3	31 ± 13

to controversial opinions (HULSE 1963) In some recent papers (HARRIS, HAIGH & KUGLER 1963, HARRIS & KUGLER 1964, 1965), it has been suggested that these cells, during recovery after irradiation, may act as stem cells

Effects on other marrow cells The data presented in Table 2 are difficult to interpret as the range of observed values is wide It seems, however, that the 'reticulum cells, the plasma cells, and the so called 'damaged' cells were unaffected by treatment The group of reticulum' cells comprised several different cell types *No differential counts of the cells included in this group were performed*

Discussion

In a previous study in rats (HØST 1966a) differences were demonstrated in the recovery pattern of granulocytes *in* the peripheral blood after treatment with cyclophosphamide and after total body irradiation, respectively

The present study confirmed that cyclophosphamide produces only a short-lived depression of myelopoiesis, followed by an overshooting myeloid cell production, while roentgen irradiation causes a more long lasting suppression of myelopoiesis, interrupted by an abortive rise It was found however that

the lymphocyte like marrow cells exceeded normal numbers during recovery after irradiation, while the recovery of these cells in the cyclophosphamide treated animals was more protracted The erythroid cell precursors demonstrated an almost similar rapid and apparent complete recovery after both irradiation and cyclophosphamide

The similarity in the response of erythropoiesis may seem difficult to reconcile with the difference in response of myelopoiesis However the following explanation may be put forward Both irradiation and cyclophosphamide will affect the reproductive integrity of the marrow cells According to LAJTHA (1961) the irradiation effect may demonstrate itself in the following ways (1) temporary delay in mitosis (2) permanent inhibition of mitosis and giant cell formation (3) death of cell before entering mitosis and (4) death after a few mitoses LAJTHA furthermore predicted the theoretically expected effect of a single dose of radiation on marrow cells in terms of a simplified scheme for the bone marrow cell population The radiation induced mitotic delay will decrease the numbers of dividing marrow cells Later when these cells have been depleted, the feed into more mature non dividing cells will be reduced The latter marrow cells will also decrease in number as their entry into peripheral blood remains unchanged

The stem cells will continue to differentiate into the dividing-compartment but as these cells also have received the same dose of radiation the subsequent mitosis may be delayed and interphase death may occur An abortive recovery may follow after cessation of the mitotic delay induced by radiation Cells may enter mitosis but many of them depending upon the dose of radiation received have lost their reproductive integrity and will undergo only one or two mitoses The result will be a suboptimal temporary rise in their numbers After a time lag depending upon the radiation dose *the stem cells will regenerate and increase to the normal population level, and complete recovery will follow* The pattern observed in the present study of myeloid cell response corresponds well with the above hypothesis as regards the irradiation effect on marrow cells

On the basis of this pattern of myeloid regeneration after cyclophosphamide it would appear that no reduction in the reproductive integrity persisted after cessation of the induced mitotic delay i e the damage to the stem cells was less marked than that to the dividing compartment There will thus be quick recovery with a temporary overshoot in myelopoiesis, owing probably to increased demand for granulocytes but without any secondary failure of myelopoiesis

Regeneration of erythropoiesis followed a fairly steady course both after irradiation and cyclophosphamide and occurred apparently without any abortive

rise This may indicate that no reduction in reproductive integrity of the erythroid precursors occurs after cessation of the mitotic delay induced by either cyclophosphamide or radiation Another possible explanation may be that the demand for red cell production did not exceed the capacity for erythropoiesis, even if the latter was reduced If so, possible differences in the restitution of erythropoiesis after irradiation and after cyclophosphamide may be revealed by an artificially increased demand for red cell production According to experimental data now in hand, such differences are indeed present (HOST, under preparation)

It has previously been shown that total body irradiation (350 R) had a more depressive effect on lymphocytes in peripheral blood than cyclophosphamide (50 mg/kg bodyweight) (HOST 1966 a) The lymphocytes did not regain pre treatment levels within 3 to 4 weeks after irradiation, while in the cyclophosphamide treated animals such values were obtained in 10 to 14 days The present results, together with those reported earlier, indicate that after cyclophosphamide the recovery of the lymphocytes in peripheral blood possibly ran simultaneously with that of the lymphocyte like marrow cells In the irradiated animals, however, the recovery of these cells in peripheral blood and bone marrow, respectively, occurred with a 2 week interval This observation may suggest that the cells observed in blood and marrow, during recovery after total body irradiation, are different cells with different functions but with almost similar morphologic characteristics The marrow lymphocytes have been claimed to act as stem cells during recovery after irradiation in guinea pigs (HARRIS, HAIGH & KUGLER 1963, HARRIS & KUGLER 1964, 1965) If these cells act as stem cells, one would expect them to precede the other marrow cells in recovery The present study indicates that in the cyclophosphamide treated animals the regeneration of the myeloid and the erythroid cells preceded that of the lymphocyte like marrow cells by at least 4 to 6 days In the irradiated animals, the initial regeneration of the myeloid and the erythroid cells also occurred prior to the regeneration of the lymphocyte like marrow cells A secondary failure of myelopoiesis occurred, however, and the final regeneration did not take place within the period covered by the present investigation The accumulation of the lymphocyte like marrow cells may therefore be of significance in the final regeneration of the myelopoiesis

Taken together, the present data indicate that in cyclophosphamide treated animals the lymphocyte like cells are of slight significance for the final recovery of the myeloid and erythroid cells In irradiated animals, on the other hand, the lymphocyte like cells may play a part in the final regeneration of the myeloid cells

Acknowledgements

This work was supported by the Norwegian Cancer Society The author takes this opportunity of thanking Mrs I Gulliksen for technical assistance

SUMMARY

Comparative studies of the effect of cyclophosphamide or total body irradiation on bone marrow cells have been performed in rats The recovery of erythropoiesis was the same after the two types of treatment whereas differences were evident in the pattern of myeloid regeneration It is suggested that the stem cells are less damaged by cyclophosphamide than is the dividing compartment whereas the reproductive integrity of the stem cells is still reduced after cessation of the radiation induced mitotic block

ZUSAMMENFASSUNG

An Ratten wurde der Effekt von Cyclophosphamidverabreichung mit dem Einfluss der Totalbestrahlung auf das Knochenmark verglichen Nach Anwendung beider Methoden war die Erholungsbereitschaft der Erythropoese die gleiche aber es bestanden deutliche Unterschiede in der Regeneration des myeloiden Gewebes Es erscheint dass der Zellstiel sich nach Cyclophosphamidverabreichung rascher erholt als der Teil der Zelle in der die Zellteilung vor sich geht nach der Blockierung der Mitose durch Bestrahlung bleibt jedoch die Reproduktionsfähigkeit des Zellenstieles vermindert

RÉSUMÉ

L auteur a fait sur des rats des études comparatives de l effect du cyclophosphamide et de l irradiation totale du corps sur les cellules de la moelle osseuse La restauration de l érythropoïese a été la même apres ces deux types de traitement alors qu il y a eu des differences évidentes dans l aspect de la régenération myéloide L auteur pense que les cellules souches sont moins lésées par le cyclophosphamide que les cellules en division alors que le pouvoir reproducteur des celles souches est encore réduit apres la cessation du blocage mitoque du aux radiations

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DOSE DISTRIBUTION STUDIES IN EXTERNAL IRRADIATION OF CARCINOMA COLLI UTERI

by

NILS ERIK RANUDD

Comparisons between different treatment techniques and precalculation of the radiation effects should preferably be based on the energy absorbed in the tissue in question. This can be visualized conveniently with dose distribution diagrams giving the absorbed dose in rads. As a basis for comparison of various irradiation techniques, a description of the techniques used at Radiumhemmet in the external treatment of carcinoma of the cervix will be given in this paper.

Terminology and definitions are those proposed by the International Commission on Radiological Units and Measurements (ICRU 1963).

Extension of the tumour. According to KOTTMEIER & VARA (1963) carcinoma of the uterine cervix may start in any part of the cervix or portio. From their origin in the epithelium the changes extend either exofytically towards the vagina or infiltrate the underlying tissue. The growth is relatively fast in other parts of portio, fornices, vaginal wall and the parametrium, parametrial

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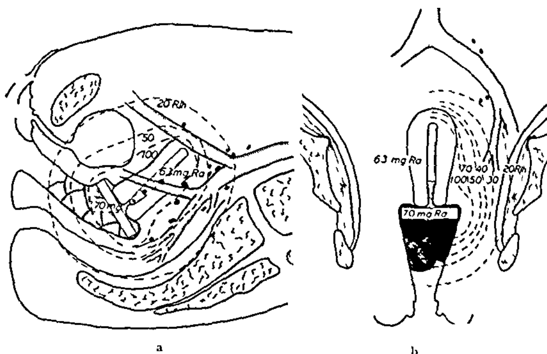


Fig 1 Dose distribution from a radium application in a medial cross section of the patient (a) and in a plane through the *uterus* and perpendicular to the sagittal plane (b) Vena iliaca interna externa and obturatoriae are projected in these planes

extension occurs often very early In about 60 % of all cases, where the growth is clinically limited to the cervix, histologic investigation reveals neoplastic tissue in the parametrium An early spread along the lymph vessels (18 % in stage I) to the regional lymph nodes usually occurs In spite of the rapid spread in the parametrium and the regional lymph nodes the changes are limited for a comparatively long time to the lesser pelvis (KOTTMEIER & VARA 1963)

The region that may in all probability contain malignant growth is outlined in Fig 1 where the vena iliaca externa and interna and vena obturatoriae are projected in a medial plane as well as one through the uterus

Intracavitary irradiation

Studies of the dose distribution in the pelvis in intracavitary radium treatment of cancer of the cervix according to the Stockholm technique have been published elsewhere (SIEVERT 1932, KOTTMEIER 1951 and 1964, WALSTAM 1954, KJELLGREN & RAGNHULT 1963)

The dose distribution from a typical intracavitary radium application is

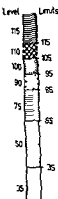


Fig 2 Shading code for the dose levels

illustrated in Fig 1 The dose decreases rapidly with the distance from the source In this example the dose in nodi lymphatici obturatoriae and nodi iliaci externi is only about 25 % of the dose 2 cm from the cervical channel about 30 % of the dose in the posterior bladder wall or about 50 % of the dose in the anterior wall of the rectum This implies that the regional lymph nodes cannot be given an adequate dose with the intracavitary irradiation alone without causing over dosage in tissues nearer the source e g the bladder and rectum (KOTTMEIER 1964) At Radiumhemmet the intracavitary irradiation is therefore combined with external irradiation in all cases of carcinoma of the uterine cervix preclinical carcinoma stage I A excepted

External irradiation

Radiation quality At Radiumhemmet almost all external irradiation until 1957 was performed with orthovoltage roentgen techniques The radiation qualities used had a HVL in the range 0 5 to 2 0 mm Cu and the SSD was 50 to 60 cm Since 1957 when the first kilocurie cobalt 60 unit Gammatron 1 was installed (HULTBERG et coll 1959) an increasing number of patients have been treated with cobalt 60 radiation The experience from treatment with orthovoltage roentgen rays is not directly applicable to telecobalt therapy in so far as calculation of exposure is concerned Among the advantages of cobalt 60 gamma radiation over orthovoltage are the build up of the absorbed dose causing a skinsparing effect the higher percentage depth dose and the lower absorption in bone tissue The last two effects are evident from the illustrations There are possibly also differences in the relative biologic effect (RBE) which may be 10 to 30 % higher for the roentgen qualities considered here than for cobalt 60 gamma radiation (PATERSON 1960)

Calculation procedure In order to facilitate comparison between the various dose distribution diagrams the doses are expressed as percentages of the absorbed dose at a point 5 cm from the pelvic midline This point corresponds to the so-called point B (TOD & MEREDITH 1953) The dose at this point is named the target dose Fig 2 shows the shading code used to illustrate the dose distribution in subsequent figures This code is adjusted to irradiation with cobalt 60 radiation where it is considered desirable to plan the treatment so that the dose is within ± 5 % in the target volume

SSD=50 cm
A-75x15cm
170 %
170
150
130
125
110
145
100
75
90
50
195
130
280
150
170
DOSE %
100
90
80
70
60
50
40
30
15
20
25
30
DOSE AT POINT B AS A PERCENTAGE OF GIVEN DOSE
ANT POST DIAM cm
SSD=50 cm 170 %
A 75x15 cm

Fig 3 The left hand side of the figure illustrates the dose distribution in a horizontal cross section 10 cm above the symphysis when using a technique with compressing tubes The dependence of the target dose on the patient thickness is shown to the right

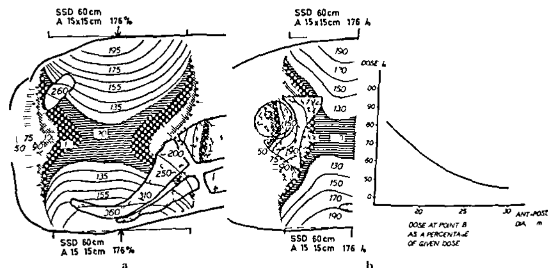


Fig 4 Dose distribution in a medial cross section (a) and in a horizontal cross section 5 cm above the symphysis (b) by using two opposed beams (HVL = 1 0 mm Cu) On the right hand side of 4b the dependence of the target dose on the anterior posterior diameter of the patient is plotted

The various dose distributions are obtained by graphical summation of the standard isodose charts Calculated charts (IAEA 1962) were used for ortho voltage The isodose charts for cobalt 60 were measured with an automatic isodose recorder (LARSSON et coll 1963) fitted with an ionization chamber with an outer diameter of 4 5 mm and a length of 15 mm (BENNER et coll 1959) The ionization current was amplified with a vibrating reed electro meter

In the calculations corrections were made for the oblique incidence of the cobalt 60 beam according to the isodose curve shift method (DUTREIX and DUTREIX 1962) Consideration was paid to the different absorptions in bone and soft tissue The average density of bone tissue is assumed to be 1 3 g/cm³ (ELLIS & JONES 1957 GEST 1961) In virtue of the statements in NBS Hand books (ICRU 1959 and 1962) the relative dose reduction per cm bone tissue is esti mated to about 1 1 % for cobalt 60 radiation and about 7 % for the roentgen quality of HVL = 1 0 mm Cu The conversion factors f, from R to rad, used in these calculations are

	Muscle	Bone
Co 60	0 96 rad/R	0 93 rad/R
HVL 1 0 mm Cu	0 95 rad/R	1 93 rad/R

The antero posterior and the lateral diameters of the patient, in a horizontal cross section 5 cm above the symphysis, are chosen as 20 cm and 35 cm, respectively

Various irradiation techniques The most common and simplest techniques earlier used at Radiumhemmet are illustrated in Figs 3 to 5 From these figures it is obvious that the techniques result in a very inhomogeneous dose distribution The minimum dose in the irradiated volume is generally received by the region where the target volume is situated The maximum dose is received by regions containing the rectum the small bowels and the urinary bladder In those cases where the irradiation techniques as illustrated in Figs 4 and 5 are combined with intracavitary applicators, the urinary bladder and the rectum are protected by lead absorbers placed in the beam in front of the position of the applicator In this way it is possible to diminish the dose from the external irradiation in the most critical parts of the bladder and rectum by about 50 % For radiation qualities with HVL 1 0 mm Cu the energy absorption per gram bone tissue (absorbed dose) is about twice as high as that of soft tissue The energy absorption per gram tissue from ⁶⁰Co radiation is on the other hand somewhat lower in bone than in wet tissue In the irradiation of the pelvic walls with this technique and conventional

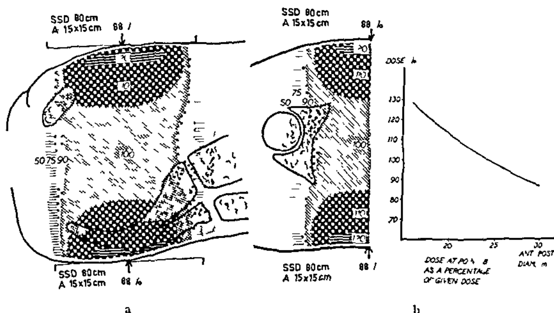


Fig 5 Dose distribution from two opposed cobalt 60 beams in a medial cross section (a) and in a horizontal cross section 5 cm above the symphysis (b) On the right hand side of 5b the dependence of the target dose on the antero posterior diameter of the patient is plotted

roentgen rays, those parts of the head and neck of the femur that are in the beam will receive appreciable doses, 70 to 150 % in the case illustrated in Fig 4 and 150 to 200 % in Fig 3 When opposed beams are used, the resulting dose distribution depends very much on the patient diameter along the central ray In order to illustrate this, the target dose as a percentage of the given dose is plotted as a function of the patient's a p diameter in Figs 3, 4b and 5b From these diagrams it is clear that it is not sufficient to state the given dose only, especially when orthovoltage radiation qualities are used

With moving beam techniques (Dahl & Vikterlof 1960) or suitable combination of several fixed beams it is however possible to obtain a better dose distribution with the maximum dose in the target volume and a rapid decrease of dose towards critical organs such as the bladder and rectum

In cases where the growth has spread into the vagina and the paravaginal tissue it is more difficult to obtain a sufficiently large and homogeneous dose in the total target volume With the techniques described the lower boundary of the beams must be kept sufficiently high in the body in order to avoid tangential irradiation of the perineum This implies that there is a risk that the lower part of the vagina will receive an inadequate dose For this reason beams are sometimes directed towards the vulvae thus irradiating the lower

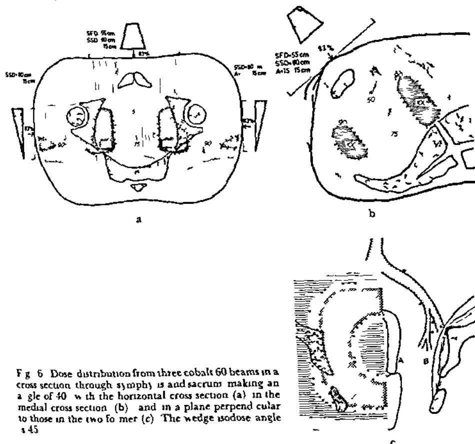


Fig 6 Dose distribution from three cobalt 60 beams in a cross section through symphysis and sacrum making an angle of 40 with the horizontal cross section (a) in the medial cross section (b) and in a plane perpendicular to those in the two former (c) The wedge isodose angle is 45

part of the vagina It is however, almost impossible to avoid local over or underdosage if too simple techniques are used

Wedge filter beams at a suitable angle in the perineal and anterior areas makes it possible to give a high and homogeneous dose to the vagina and the paravaginal tissue at least when the patient is thin The bladder and the rectum are protected by applying the beam parallel to the vagina With this technique however it is difficult to include the pelvic walls in the homogeneously irradiated region

With three beams applied equally loaded as illustrated in Fig 6 however it is possible to irradiate the paracervical and paravaginal tissues and the pelvic walls at the same time A high relative dose is obtained in the target volume with a rapid decrease of dose towards the bladder, the rectum and the small bowel Tangential irradiation of the perineum and local overdosages are

avoided The beams can easily be modified to suit the shape of the target volume All the three beams may be applied with the patient in the supine position By using a lead absorber in the anterior beam it it also easy to protect regions already heavily irradiated with intracavitary radiation sources The effect of a 4 cm high circular truncated lead cone in the anterior beam is illustrated in Fig 6

Checking the precalculation The precalculated dose distribution may easily be checked during the treatment by measurements in the vagina, the rectum and at the exit surface The measurements are at Radiumhemmet made with Bg chambers (SIEVERT 1934) The small size and the favourable physical properties of these chambers make them particularly suitable for these measurements (SIEVERT 1934, DAHL & VIKTERLOF, HULTBERG et coll 1959, SKOLDBORN 1959) When measuring in the rectum, the chambers are inserted in a flexible plastic tube and when measuring in the vagina a rigid one is used Exit dose measurements can be made to correct for inhomogeneities (SUNDBOM 1965) The positions of the beam and detectors in relation to the pelvic bones are checked with exit films in a similar way as was done by LINDELL & WALSTAM 1956 The film used is Gevaert Dipos N 51, which is so insensitive that it can be left on the exit side of the patient throughout an ordinary treatment session

The irradiation techniques described above are the principal ones used Every patient irradiation with the multifield technique worked out during the last few years is individually planned, however, and the technique is matched to the shape and position of the tumour and the geometry of the patient

Acknowledgement

The author is grateful to Prof H L Kottmeier and to Rune Walstam Ph D who suggested the investigation and offered valuable advice during its progress

SUMMARY

Various techniques for the external irradiation of carcinoma colli uteri are discussed and illustrated by dose distribution in two or three planes For external irradiation of patients who have received intracavity radium application a technique with three beams is proposed and its advantages are discussed

ZUSAMMENFASSUNG

Verschiedenartige Methode fur externe Bestrahlung des Cervixkarzinomes und deren Dosisverteilung in zwei oder drei Ebenen werden besprochen Fur Patienten die bereits intrakavitare Bestrahlung erhalten haben wird ein externer Bestrahlungsplan mit drei Feldern angegeben und die Vorteile dieses Plans erlautert

RÉSUMÉ

L'auteur examine diverses techniques d'irradiation externe du cancer du col de l'utérus et donne des exemples de distributions de doses dans deux ou trois plans. Pour l'irradiation externe des malades qui ont eu une application intracavitaire de radium, il propose une technique à trois champs et en examine les avantages.

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FROM THE DEPARTMENT OF PHARMACOLOGY, ROYAL VETERINARY COLLEGE STOCKHOLM AND THE RESEARCH INSTITUTE OF NATIONAL DEFENCE DEPT I SUNDBYBERG SWEDEN

AUTORADIOGRAPHIC WHOLE BODY STUDIES OF ^{14}C NITROGEN MUSTARD IN NORMAL AND TUMOUR BEARING MICE

by

L E APPELGREN J BACKSTROM C J CLEMEDSON, A NILSSON B SORBO and S ULLBERG

In an earlier investigation (CLEMEDSON et coll 1963) the distribution of sulphur mustard in mice was studied by whole body autoradiography It was found that the compound was fairly uniformly distributed with accumulation mainly in excretory organs

Since the nitrogen mustards have certain properties in common with the sulphur mustards we considered it of interest to study the distribution of a ^{14}C-labelled nitrogen mustard methyl dichlorethylamine, using the same autoradiographic technique The distribution of this compound in animals has previously been studied by measurements on dissected organs (see SMITH et coll 1958 MANDEL 1959 and BROWN 1963) but it could be expected that the use of the whole body autoradiographic technique would give additional information especially concerning the distribution in organs not previously studied by the dissection technique

As nitrogen mustards have found therapeutic application in the treatment of neoplastic diseases a series of tumour bearing mice was also included in the present investigation

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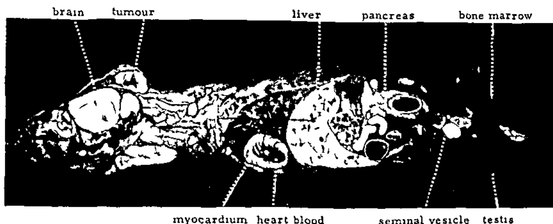
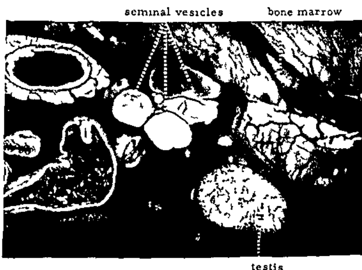


Fig 1 Autoradiograms of male mouse *Upper* At 5 min after intravenous injection of ^{14}C nitrogen mustard White areas correspond to high radioactivity the blood is rapidly cleared of labelled substance Highest uptake is seen in brain and seminal vesicles fairly high concentration in liver salivary gland myocardium and in the transplanted tumour *To the right* Detail of upper view Very high activity in the epithelium (but not in contents) of the seminal vesicles the testicular tubular walls show an intermediate concentration while the tubular lumina are void of radioactive substance



Methods The nitrogen ^{14}C mustard gas compound, methyl dichlorethyl amine with a total activity of 105μCi and a specific activity of 1 mCi/mM was obtained from CEA CEN, Centre d'études de l'energie nucleaire, Belgium, and was dissolved in 2 ml isotonic saline solution

Ten adult male CBA mice, weighing about 30 g, were used for the experiments One group of five animals had been tranplanted with small pieces of ^{90}Sr induced osteosarcomas subcutaneously in the dorsal neck region (NILSSON 1962) The tumours had been used for transplantation in several generations of animals and had lost their original content of ^{90}Sr In one month, the neoplasms had reached a diameter of about 1 5 to 2 cm

The animals were injected intravenously into a tail vein each animal receiving 0 1 ml of the mustard solution, corresponding to 1 mg mustard or

5 3 μCi This high dose, which is lethal to mice (STERNBERG et coll 1958) was used in order to obtain autoradiograms within a reasonable length of time All animals survived for the relatively short observation times (up to one hour) used in this study The animals were sacrificed under ether anesthesia at various intervals by immersion in a mixture of solid carbon dioxide and hexane (about — 70 C) The survival times in each group were 1 min 5, 10 20 and 60 minutes

The frozen animals were sectioned and autoradiograms prepared according to the method described by ULLBERG (1954 1958) Sagittal sections 20 μ thick through the whole animal were cut in a refrigerated room (— 10° C) at different levels and were dried at the same temperature The sections were pressed against Structurix (Gevaert) X ray film After an exposure time of 80 days the autoradiograms were developed and some of the sections were stained while kept on the tape

Results

There was a rapid fall of the activity in the blood, and already 1 min after the injection several soft tissues showed a higher concentration of ^{14}C than the blood This is in agreement with the observations of NADKARNI et coll (1956) The highest concentrations after 5 min were found in the kidney, central nervous system nasal mucosa, salivary glands and myocardium (Fig 1) Very few changes in this distribution picture could be seen at the longer survival times studied (Figs 3 and 4)

Urinary system Immediately after the injection the kidneys showed the highest radioactivity in the body and one hour after the injection the kidneys still showed the highest activity After 5 min the urinary bladder showed a high ^{14}C concentration which persisted throughout the whole experiment

Central nervous system One minute after the injection the activity was very high in the central nervous system with the gray matter dominating Plexus choroideus showed an intense uptake of ^{14}C mustard and so did the ganglia (Fig 3) The distribution pattern was the same one hour after the injection

Eyes A high level of ^{14}C was seen in the retina and the optic nerve at all the times studied A still higher level could be noticed in the pigment layer of the choroid (Fig 2 a and b) It was most marked from 1 to 10 min after injection and then disappeared A slight uptake was seen in the periphery of the lens (Fig 2a)

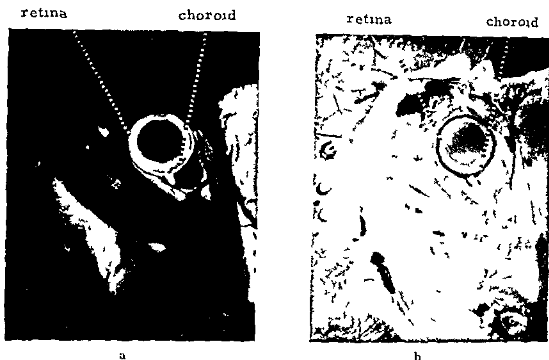


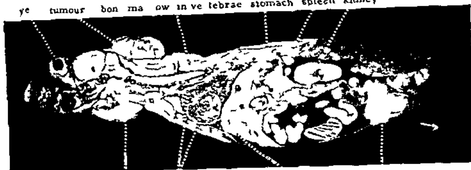
Fig 2 a) Detail of whole body autoradiogram showing eye of mouse 10 min after injection of ^{14}C nitrogen mustard Highest activity is seen in the choroid high concentration also in the retina b) Section corresponding to (a)

Digestive system The salivary glands showed relatively strong accumulation already 1 min after the injection This could still be observed after 1 hour Some radioactivity was seen in the gastric mucosa and content from 5 to 60 min

The liver showed a relatively high uptake 1 min after injection and after 5 min the excretion through the bile was apparent A biliary excretion of metabolites from nitrogen mustard has previously been demonstrated by TRAMS (1958)

The radioactivity in the pancreas increased gradually from 1 min to 60 min The intestinal mucosa showed an intermediate level of activity throughout the experiment In the mice killed after 1 hour rather high activity could be detected in the intestinal content

Circulatory system The myocardium, at all the times studied showed a higher uptake than the skeletal muscles The larger arteries (e g aorta and the pulmonary artery) were very prominent



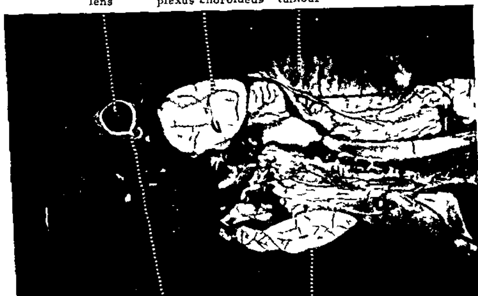


Fig 3 Aut rad ogr ms of male mouse *Upper* At 20 min after njection High concentration in eye br n kid ey and ur nary bladd bone marrow pleen and thymus show nte med ate uptake *Low* D ta l of uppe v ew H gh concent at on n retina and periphery of the lens act ty in the horoid l ye is still high In the b ain the highest activ ty s seen n the choro d plexus the grey matter has lightly h gher activ ty than the white

Respiratory system An intense accumulation was seen in the nasal region already at 1 min and the isotope concentration persisted throughout the observation period (Fig 5)

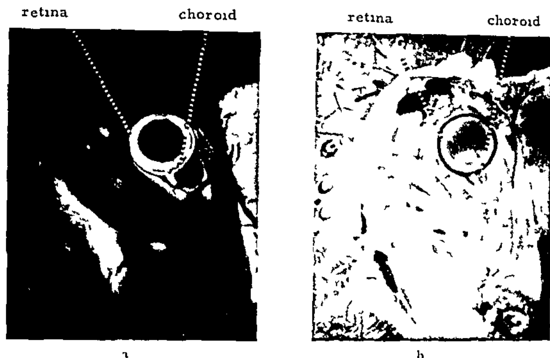


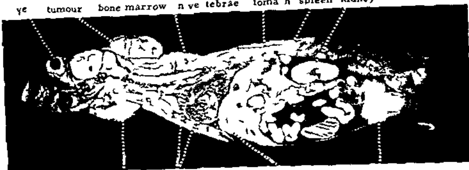
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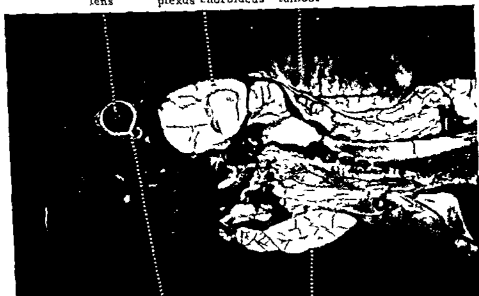


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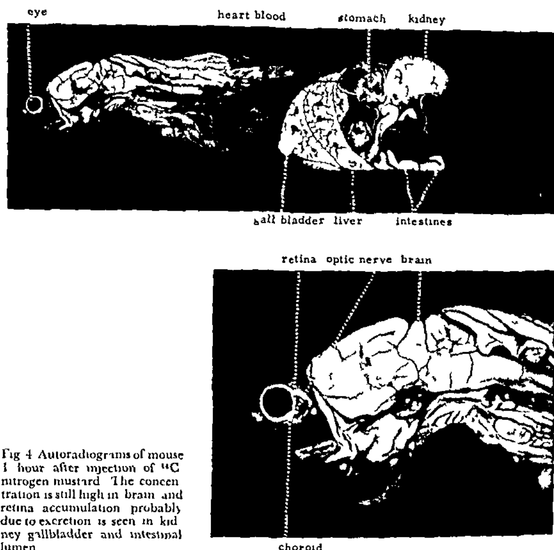


Fig 4 Autoradiograms of mouse 1 hour after injection of ^{14}C nitrogen mustard The concentration is still high in brain and retina accumulation probably due to excretion is seen in kidney gallbladder and intestinal lumen

The lung parenchyma did not show any uptake while the bronchi had an intermediate activity The pleural fluid showed some activity

The *bone marrow* showed an intermediate isotope concentration

Endocrine organs The thyroid showed a relatively high uptake of ^{14}C Five and ten minutes after the injection, thymus showed a rather high concentration which then declined slightly The adrenal showed a moderate uptake both in the cortex and medulla In the testes a very distinct pattern of the tubular walls could be seen The epididymis showed a still more marked accumulation The seminal vesicles showed a rather high activity in their glandular parts while the secretion was rather free from ^{14}C (Fig 1)

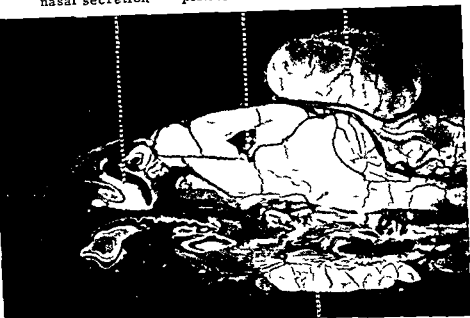


Fig 5 Autoradogram of head of mouse 1 hour after injection of C-nitrogen mustard Strong accumulation in nasal mucosa

Brown fat A high isotope concentration could be seen in the brown fat

Tumour During all the times studied the transplanted tumour had an uneven partially high isotope concentration The areas of high uptake seemed to correspond to tumour tissue with viable cells while the uptake was absent in necrotic parts

Discussion

When the distribution pattern of the ¹⁴C-nitrogen mustard is compared to that of ³⁵S sulphur mustard previously reported (CLEMEDSON et coll 1963) it is apparent that the radioactivity left the tissues much more slowly in the nitrogen than in the sulphur mustard experiment

Another remarkable difference is the much stronger tendency for ¹⁴C nitrogen mustard to accumulate in the central nervous system and also in the choroid and the retina of the eye The accumulation in the brain may be

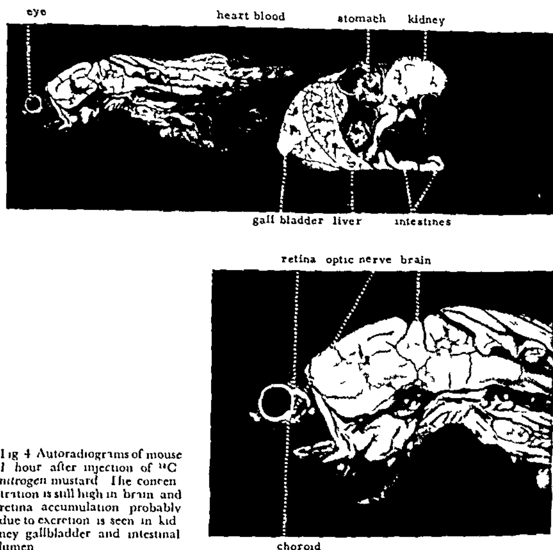


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related to the neurotoxic symptoms observed after high doses of nitrogen mustard (PHILIPS 1950, STERNBERG et coll 1958) With respect to the strong but transient deposit in the choroid it can be mentioned that a similar accumulation in the choroid was not observed in the autoradiographic study of sulphur mustard (CLEMEDSON et coll 1963) but has been found for another tertiary amine and some N substituted phenothiazines (POTTS 1962) It thus seems as if the affinity to the choroid may be ascribed to the tertiary nitrogen group

Both the ^{35}S sulphur and the ^{14}C nitrogen mustard had a strong tendency to accumulate in the nasal region, the fact that this was apparent already 1 min after injection indicates that the unmetabolized compound has an affinity to some structure in the nasal mucosa If this is of any practical consequence is not known, as any injurious effects on the nasal mucosa of parenterally administered mustards have apparently not been reported in the literature This point deserves further attention

The uptake of ^{14}C nitrogen mustard in thyroid and in blood vessel walls was remarkable A specific uptake in the thyroid was noticed also for the ^{35}S sulphur mustard

With respect to the cytostatic properties of nitrogen mustard it may be noted that organs with a rapid cell formation such as bone marrow, lymphoid tissues, testicular tubuli and the growing parts of the tumour all showed an intermediate to fairly high concentration A clear relation between rate of cell formation and affinity to the labelled compound could, however, not be established

Apparently, the uptake of labelled nitrogen mustard in tumours has not been previously studied but other alkylating agents such as triethylenephosphoramide show a moderate uptake in tumour tissue (SMITH et coll 1958)

The results from the present investigation on ^{14}C nitrogen mustard agree to a large extent with the previous findings by SKIPPER et coll (1951) on the distribution of the compound in mice as studied by determinations of radioactivity in dissected organs However, certain discrepancies are found for instance with respect to the uptake in brain and in bone marrow SKIPPER et coll thus found a low concentration of ^{14}C in the brain, and a very low concentration in bone marrow, whereas in the present work a high uptake was found in brain and a moderate uptake in bone marrow These discrepancies may be due to the lower dose of nitrogen mustard and the longer observation times (6 and 24 hours) used by SKIPPER and his co workers It may be added that the results obtained in the present investigation pertaining to brain and bone marrow are supported by recent work by others Thus MAHALEY et coll (1961) found a high uptake of labelled nitrogen mustard in certain regions of the brain in dogs, and MELLETT & WOODS

(1960) have demonstrated by a fluorometric technique a relatively high concentration of unchanged nitrogen mustard in the bone marrow of dogs after intravenous injection of the compound

Finally it should be pointed out that a considerable fraction of the isotope localized by autoradiography (and by measurements on dissected organs) may be present not as the parent compound but as metabolites For a discussion of the metabolism of the nitrogen mustard see reviews by SMITH et coll 1958 MANDEL 1959 and BROWN 1963

SUMMARY

The ^{14}C-labelled nitrogen mustard methyl-dichlorethylamine was given by intravenous injection to mice and the distribution at various times was studied by whole body autoradiography An accumulation of the radioactive substance was found in the excretory organs and in the central nervous system the choroid and retina of the eye the nasal mucosa blood vessel walls the thyroid and the growing parts of transplanted tumours

ZUSAMMENFASSUNG

Mit ^{14}C gezeichnetes Nitrogen Mustard Methyl-dichlorathylamin wurde Mausen iv injiziert und die Verteilung zu verschiedenen Zeitpunkten mittels Ganzkorperradiographie studiert Es wurde eine Anhaufung der radioaktiven Substanz in folgenden Organen gefunden in den Exkretionsorganen im ZNS in der Choroidea und Retina des Auges in der Nasenschleimhaut den Wanden der Blutgefässe der Schilddruse und den wachsenden Teilen von transplantierten Tumoren

RÉSUMÉ

Une ypérite azoteé marquée au ^{14}C la méthyl dichloréthyl*amine a été administrée* par voie intraveineuse a des souris et sa distribution a été etudiée a divers moments par autoradiographie de tout le corps On a observé une accumulation de la substance radioactive dans les organes excréteurs et dans le systeme *nerveux central* la choroide et la retine de l oeil la muqueuse nasale les parois des vaisseaux sanguins la thyroide et les parties en croissances des tumeurs transplantees

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EFFECTS OF SOME RADIOPROTECTIVE SUBSTANCES UPON PRE NATAL SURVIVAL OF OFFSPRING TO ROENTGEN IRRADIATED MALE MICE

by

H FROLEN

Since KAPLAN & LYON (1953) published their report on experiments in which mercaptoethylamine was used in an attempt to protect the hereditary material against ionizing radiation, an increasing number of experiments with a similar goal have been reported The greater number of these later works have however not primarily been intended as studies of the purely genetic consequences of irradiation but have rather been concerned with clarifying the ability of different substances to prevent radiation induced changes in the individuals reproductive mechanism Thus RUGH & WOLFF (1957) showed that the sterility effects following irradiation of ovaries could be diminished with the help of chemical agents and two years later WANG, KUSKIN & RUGH (1959) reported that cysteamine had similar effects on males MANDL in two experiments from 1959 found that degeneration of gametes following irradiation was partly prevented by prophylactic treatment with mercaptoethylamine Histologic studies showed that radiation damage to female gametes appeared in lower frequencies following a similar pretreatment

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Table 3

Irradiated spermatozoa protected by cysteamine (albino)

Series	Dose	Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Survival frequency a
		Cysteamine					
1	0 R	75	157	974	57	2	94.29
2	200 R	75	140	755	151	5	82 88
3	400 R	75	145	650	231	9	73 03
		NaCl					
1	0 R	75	145	844	58	0	93 64
2	200 R	75	160	817	187	5	80 97
3	400 R	75	118	475	211	0	69 24

EHLING (1964) The experiments now to be reported have been in progress since 1962 and may be considered as complementary tests of genetic effects of radioprotective substances known to be somatically functional

Material and Methods In all but one experiment, highly inbred CBA males have been used The exceptional experiment was made with males from a non-inbred Albino strain to test the protective effect of cysteamine on the genetical material of males more sensitive to irradiation than CBA males (FROLÉN 1965)

The males were irradiated when about 70 days old There was always a control group of the same size as the test groups given various agents In the control the males were given saline solution All injections were given intra peritoneally 15 min before irradiation 4 mg of the substance (cysteamine cystamine AET, glutathion or serotonine) in 0 4 ml saline Each injected group was subdivided into three parts which were given different amounts of irradiation When not otherwise stated the dose levels were 0 R, 300 R and 600 R given as whole body irradiation The roentgen equipments was a Muller MG 300 apparatus operated at 160 kV and 10 mA with filters 0 5 mm Cu + 4 mm Al The dose rate was 84 R/min The distance between tube and object was 40 cm

The genetic effects, determined as the rate of intrauterine death of offspring to the irradiated males was studied in matings within the first week (spermatozoa) and the third week (spermatids) respectively

Table 1

Irradiated spermatozoa protected with cysteamine (CB 1)

Series	Dose	Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Survival frequency %
		Cysteamine					
A	0 R	60	146	867	113	6	87.93
B	300 R	60	139	679	201	4	77.27
C	600 R	60	127	487	259	2	65.11
		NaCl					
A	0 R	60	140	848	108	4	88.33
B	300 R	60	140	650	236	3	73.12
C	600 R	60	121	387	273	0	58.64

Table 2

Irradiated spermatids protected with cysteamine (CB 1)

Series	Dose	Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Survival frequency %
		Cysteamine					
A	0 R	60	148	974	80	4	90.17
B	150 R	60	128	661	157	2	80.61
C	300 R	60	121	434	213	5	60.56
D	600 R	60	44	79	76	0	50.97
		NaCl					
A	0 R	60	137	880	83	2	91.19
B	150 R	60	108	510	154	6	76.12
C	300 R	60	87	271	190	1	58.66
D	600 R	60	28	41	57	0	41.83

The positive effects of radioprotective substances in a genetical test were first shown in 1961 by LÜNING, FROLÉN & NELSON. There cysteamine reduced the mutation rate in spermatozoa by an estimated 25 %. Since then, similar experiments have been reported by LEONARD & MAISIN (1963, 1964) and

Table 5

Irradiated spermatozoa protected with cystamine (CBA)

Series	Dose	Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Survival frequency
		Cysteamine					
A	0 R	60	150	839	116	10	86 94
C	300 R	60	134	517	193	0	72 82
D	600 R	60	137	401	269	1	59 76
		NaCl					
A	0 R	60	151	851	104	6	88 55
C	300 R	60	150	599	239	6	70 97
D	600 R	60	103	314	182	3	62 92

Table 6

Irradiated spermatozoa comparison between cysteamine and AET (CBA)

Ser	Dose	NaCl Irrad ♂♂	Preg nant ♀♀	Foe tuses	Moles	Late deaths	Surv f eq	Cysteam ne Irrad ♂♂	Preg nant ♀♀	Foe tuses	Moles	Late deaths	Surv freq
A	0 R	42	102	603	53	3	91 23	42	99	620	44	4	86 83
C	300 R	42	79	353	115	3	74 95	42	91	415	146	1	73 84
D	600 R	42	92	296	218	3	55 12	42	92	318	172	4	64 37
		AET											
A	0 R	42	95	550	66	7	88 29						
C	300 R	42	105	474	138	4	76 94						
D	600 R	42	90	265	194	4	57 24						

Table 4

Irradiated spermatozoa protected by AET (CBA)

Series	Dose	Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Survival frequency %
		AET					
A	0 R	60	124	781	67	7	91 35
C	300 R	60	107	555	158	4	77 41
D	600 R	60	92	316	199	3	61 00
		NaCl					
A	0 R	60	127	786	83	10	89 42
C	300 R	60	107	516	175	4	74 24
D	600 R	60	100	344	214	1	61 54

Each male was mated to 3 females from the CBA strain In tests of effects on spermatozoa the males were mated immediately after irradiation while in spermatid tests, they were withheld from matings for 14 days after the irradiation

The females' uterine contents were analysed on the 17th or 18th day after start of mating The number of living fetuses, dead embryos and placental resorptions (moles) was recorded for each female From these data the rate of intra uterine death was calculated The corpora lutea were not counted

Results

The results are presented in Tables 1—11 Table 1 refers to an earlier report of Luning et coll (1961)

The mutation reducing effects of the substances are reflected by the frequencies of living embryos on the 18th day of pregnancy This parameter, the survival frequency, has been computed as the percent living of total implantations, and is presented in the right hand columns of the tables These figures represent those individuals whose paternal genome had escaped lethal damages of irradiation and control conditions The material does not give any information as to what extent the chances of survival of very young non implanted zygotes have been influenced by the substances, since an analysis of the number of eggs released by the female has not been made There was, however, a dose dependent decrease in implantation rate

Table 5

Irradiated spermatozoa protected with cystamine (CBA)

Series	Dose	Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Survival frequency %
		Cysteamine					
A	0 R	60	150	839	116	10	86 94
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C	300 R	60	150	599	239	6	70 97
D	600 R	60	103	314	182	3	62 92

Table 6

Irradiated spermatozoa comparison between cysteamine and 4ET (CBA)

Ser	Dose	NaCl Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Surv freq	Cysteamine Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Surv freq
A	0 R	42	102	603	53	3	91 23	42	99	620	44	4	86 83
C	300 R	42	79	353	115	3	74 95	42	91	415	146	1	73 84
D	600 R	42	92	296	218	3	55 12	42	92	318	172	4	64 37
		AET											
A	0 R	42	95	550	66	7	88 29						
C	300 R	42	105	474	138	4	76 94						
D	600 R	42	90	265	194	4	57 24						

Table 7

Irradiated spermatozoa: comparison between cysteamine and AET — same males as in table 6

		NaCl						Cysteamine					
Ser	Dose	Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Surv freq %	Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Surv freq %
A	0 R	42	107	664	58	2	96 71	42	100	621	52	2	90 80
C	300 R	42	72	175	163	1	51 62	42	81	223	169	3	56 46
D	600 R	42	15	21	26	0	44 68	42	33	59	53	0	52 68
		AET											
A	0 R	42	103	667	48	5	92 64						
C	300 R	42	84	221	169	5	55 95						
D	600 R	42	38	53	71	0	42 74						

Table 8

Irradiated spermatozoa protected by glutathion (CB 1)

		Glutathion					
Series	Dose	Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Survival frequency
A	0 R	60	105	680	51	2	92 77
B	300 R	60	119	558	174	5	75 72
C	600 R	60	118	369	285	4	65 08
		NaCl					
A	0 R	60	120	741	64	4	91 60
B	300 R	60	125	620	142	5	80 84
C	600 R	60	131	438	268	2	61 87

Table 9

Irradiated spermatozoa protected by serotonine (CBA)

Series	Dose	Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Survival frequency
		Serotonine					
A	0 R	40	88	600	42	13	91 60
B	300 R	40	93	450	140	5	75 63
C	600 R	40	85	233	216	4	51 43
		NaCl					
A	0 R	40	83	543	66	4	88 58
B	300 R	40	90	465	130	5	77 50
C	600 R	40	78	270	193	3	57 94

Table 10

Irradiated spermatids protected by serotonine (CBA)

Series	Dose	Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Survival frequency
		Serotonine					
A	0 R	40	94	653	54	8	91 33
B	300 R	40	66	224	122	0	64 74
C	600 R	40	36	48	56	0	46 15
		NaCl					
A	0 R	40	94	652	63	8	90 18
B	300 R	40	81	196	191	4	50 13
C	600 R	40	30	46	46	3	48 42

Table 7

Irradiated spermatozoa, comparison between cysteamine and AET — same males as in table 6

		NaCl						Cysteamine					
Ser	Dose	Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Surv freq %	Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Surv freq %
A	0 R	42	107	664	58	2	96 71	42	100	621	52	2	90 80
C	300 R	42	72	175	163	1	51 62	42	81	223	169	3	56 46
D	600 R	42	15	21	26	0	44 68	42	33	59	53	0	52 68
		AET											
A	0 R	42	103	667	48	5	92 64						
C	300 R	42	84	221	169	5	55 95						
D	600 R	42	38	53	71	0	42 74						

Table 8

Irradiated spermatozoa protected by glutathion (CBA)

		Glutathion					
Series	Dose	Irrad ♂♂	Pregnant ♀♀	Foetuses	Moles	Late deaths	Survival frequency %
A	0 R	60	105	680	51	2	92 77
B	300 R	60	119	558	174	5	75 72
C	600 R	60	118	369	285	4	65 08
		NaCl					
A	0 R	60	120	741	64	4	91 60
B	300 R	60	125	620	142	5	80 84
C	600 R	60	131	438	268	2	61 87

comparisons of survival frequencies within each experiment show, as expected, a sharply reduced embryo survival at higher radiation dosages.

The reduction of the survival frequency is of the same magnitude in the treated groups as in the control groups within each series in all cases except that comprising tests of cysteamine (Tables 1, 2, 3, 5 and 7).

This implies that AET, cysteamine, glutathion and serotonine, which all have a relatively good protective effect, are genetically without effect. Cysteamine on the other hand has a rather good protective effect on both spermatozoa and spermatids. Table 3 shows the effect of cysteamine on spermatozoa from the heterozygous albino population. With regard to the great somatic radiosensitivity of these animals a different dose scale has been used than that applied to the CBA animals. The effect of the protective substance, as is seen from the survival frequencies, is only suggested.

Discussion

The frequency of occurrences which can lead to embryonic death, i.e. spontaneous and radiation-induced lethal damage, is generally supposed to have a *Poisson distribution*. The survival frequency in each series, i.e. the frequency of zygotes whose irradiated genome has escaped lethal mutation can thus be expressed with a factor e^{-m} in the frequency function. In this expression e = the natural logarithm base and m = the mean for the number of lethal factors per genome at a given dose. As an example the treatment of data from Table 2 shows the following:

Dose	*Cysteamine*	*NaCl*
0 R	$e^{-m} = 0.9017$	$e^{-m} = 0.9119$
	$m_1 = 0.104$	$m_2 = 0.092$
150 R	$e^{-m} = 0.8061$	$e^{-m} = 0.7612$
	$m_3 = 0.216$	$m_4 = 0.271$
300 R	$e^{-m} = 0.6656$	$e^{-m} = 0.5866$
	$m_5 = 0.407$	$m_6 = 0.533$
600 R	$e^{-m} = 0.5097$	$e^{-m} = 0.4183$
	$m_7 = 0.674$	$m_8 = 0.871$

The ratio $m_1 : m_2$ expresses the relationship between the mean number of spontaneous lethals per genome for the non-irradiated cysteamine-treated males compared with the same mean for the series NaCl-treated animals. Theoretically, this ratio should be equal to 1 if the cysteamine per se did not

Table 11

M value for the different substances $1 - \frac{m_1 - m}{m_3 - m_4} = M$

Strain	Data from table	Dose	Substance	Gamete stage	m_1	m_2	m_3	m_4	M
CBA	1	300	Cysteamine	Spermatozoa	0 258	0 129	0 313	0 123	0 321
	1	600			0 429	0 129	0 534	0 123	0 270
	2	150		Spermatids	0 216	0 104	0 271	0 092	0 374
		300			0 407	0 104	0 533	0 092	0 213
		600			0 674	0 104	0 871	0 092	0 263
ALB	3	200		Spermatozoa	0 118	0 060	0 211	0 066	0 117
		400			0 314	0 060	0 368	0 066	0 159
CBA	4	300	AET		0 256	0 090	0 298	0 112	0 108
		600			0 494	0 090	0 485	0 112	−0 083
	5	300	Cystamine		0 317	0 139	0 343	0 120	0 202
		600			0 515	0 139	0 463	0 120	−0 096
	6	300	Cysteamine		0 303	0 141	0 287	0 091	0 173
		600			0 440	0 141	0 595	0 091	0 407
		300	AET		0 262	0 124	0 287	0 091	0 296
		600			0 558	0 124	0 595	0 091	0 106
	7	300	Cysteamine	Spermatids	0 572	0 096	0 661	0 086	0 172
		600			0 641	0 096	0 806	0 086	0 243
		300	AET		0 571	0 076	0 661	0 086	0 139
		600			0 850	0 076	0 806	0 086	−0 075
	8	300	Glutathion	Spermatozoa	0 278	0 075	0 213	0 088	−0 624
		600			0 430	0 075	0 480	0 088	0 094
	9	300	*Serotonine*		0 279	0 088	0 254	0 121	−0 436
		600			0 664	0 088	0 545	0 121	−0 358
	10	300		Spermatids	0 434	0 090	0 693	0 103	0 417
		600			0 773	0 090	0 725	0 103	−0 098

$m = m_X$ bst $\qquad m_3 = m$ X CI

$m_2 = m_{0 sub t}$ $\qquad m_4 = m$ X CI

Earlier studies (FROLEN 1965) showed the spontaneous intrauterine death rate for our CBA strain to be about 10 % This has been reconfirmed by the present investigation As is evident from a comparison of the survival frequencies in the control groups, and the corresponding frequencies for treated animals in the non irradiated series, neither cysteamine, cystamine, AET, glutathion nor serotonine per se have had detrimental effects on embryonic survival For all the non irradiated groups it is approximately 90 % Parallel

different stages of spermatogenesis as shown with cytological techniques In addition EHLING (1964) in dissection results following AET injection of the fathers, found a higher survival frequency among foetuses conceived in the 1st to 3rd weeks after irradiation The material is comparatively small, and a breakdown into results for the different weeks is not given It is mentioned however that the effect was most marked for the 3rd week These later embryos are derived from cells which at the time of irradiation were for the most part in the spermatid stage A substance with a relatively small protective effect could because of variations in a small material give partially contradictory results such as we have found for AET

The possibility that this substance has a certain protective effect is therefore not excluded it is however considerably less than that of cysteamine

From the comparisons now presented between the effectiveness of different somatic radio-protectors, as genetic radio protectors, it is apparent that there does not necessarily exist a correlation between the genetic and the somatic protective effect

In the event that substances with a somatic protective effect are put into practical use it is of great importance to examine the consequences of such usage from a genetic point of view, since it has now been further documented that such protective effects are possible

Acknowledgement

The author wishes to express his sincere thanks to Professor K G Luning for his great inter st in the work and to Mr O Hertzberg for profitable statistical discussions

SUMMARY

The genetic radio-protective effects of cysteamine AET cystamine glutathion and *serotonine* ha e been studied Only cysteamine showed a clear mutation reducing effect on sperma tids and spermatozoa

ZUSAMMENFASSUNG

Die genetisch strahlenschutzenden Wirkungen von Cysteamin AET Cystamin Glutathion und Serotonin wurden studiert Nur Cysteamin zeigte eine eindeutige mutationsherabsetzende Wirkung auf Spermatiden und Spermatozoen

RÉSUMÉ

L auteur a étudié l effet *radioprotecteur* génétique de la cystéamine de l AET de la cystamine du glutathion et de la sérotonine Seule la cystéamine réduit nettement le nombre des mutations sur les spermatides et les spermatozoïdes

have any effect on the mutation frequency. The value obtained is 1.13, which in this case does not comprise a significant deviation from the expected ratio.

The other m values contain two different components, one of which corresponds to the control values m_1 and m and the other which is caused by irradiation. Only this radiation induced portion should be used as a basis for judging the protective effect of a substance. An estimate of this radiation induced portion may be obtained by subtracting the m values for the non irradiated groups from the corresponding series. A practical measurement of the protective effect can thus be computed by the formula

$$M = 1 - \frac{m_{x_{\mathrm{subst}}} - m_{0\ \mathrm{subst}}}{m_{x_{\mathrm{NaCl}}} - m_{0\ \mathrm{NaCl}}}$$

where x indicates an irradiated series and 0 the corresponding non irradiated series. If the tested substance is without effect then the value of M will be around 0. The greater the positive value of M obtained, the greater the genetically protective effect of the substance. On the other hand a high negative M value would indicate that the substance had a mutation enhancing effect.

If one accepts the M value as the best expression of a certain substance's mutation reducing effect at a certain dose, then we can see from Table 11 that cysteamine alone among these five somatically effective radio protectors has a clear protective effect on the hereditary material at all dose levels and gamete stages tested.

The data obtained in the experimental series with cysteamine give, as mentioned above, a convincing picture of the genetically radio protective effects of the substance. Within comparable groups, however, there are great differences. In the series comprising irradiated spermatozoa (Tables 1 and 6) one finds that in one case the M value at 300 R is 0.321 and at 600 R 0.270, while the corresponding data from a later repetition gives M = 0.173 and 0.407 respectively. In the first case the mutation reducing effect is greater at the lower dose, but in the later experiment the protective effect at the higher dose is more than double that at the lower dose.

In the series comprising cysteamine protected spermatids the same pattern was found in the repetition as in the first experiment at doses 300 R to 600 R. At a dose of 150 R, however, the protector was of considerably greater effectivity. The varying results in the spermatozoa tests are difficult to explain logically. Random influences in combination with a certain heterogeneity in the animal material may have contributed, and so may the fact that the irradiations were performed with a 6 month interlude.

The three AET series show partially contradictory results. According to LEONARD & MAISIN (1963), this substance has a certain protective effect on

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OXYGEN TENSION DISTALLY TO A TEMPORARY OCCLUSION OF THE PULMONARY ARTERY DURING OXYGEN BREATHING

by

BJORN NORDENSTROM INGRID NORDEN and ÅKE NORHAGEN

Experimental investigations have led to the general opinion that oxygenation of tumour cells may increase the effect of ionizing irradiation This was first shown by CRABTREE & CRAMER (1933) Histologic investigations of bronchial carcinomas (THOMLINSON & GRAY 1955) observations with UV microscopy of the cytologic and cytochemical structure in cells belonging to tumour cell formations (CASPERSSON & SANTESSON 1942) and histologic studies of pre operatively radiated rectum carcinomas in man (HULTBORN 1954) have all been performed Investigations have also revealed that by increasing distance from a well oxygenated stroma the cells in a tumour become protected from the effect of ionizing radiation Clinical quantitative measurements of oxygen tension in different parts of superficial tumours (CATER et coll 1957 1958 1960) have disclosed the differences that may exist The principle that increased O_2 tension bears a direct relationship to increased cell damage from irradiation has in the past ten years been applied in radiotherapy

Tumours in man that have been accessible for measurements of oxygen tension by the oxygen cathode technique such as dermal mammary and

Submitted for publication 9 November 1964

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Experimental investigations have led to the general opinion that oxygenation of tumour cells may increase the effect of ionizing irradiation. This was first shown by CRABTREE & CRAMER (1933). Histologic investigations of bronchial carcinomas (THOMLINSON & GRAY 1955), observations with UV microscopy of the cytologic and cytochemical structure in cells belonging to tumour cell formations (CASPERSSON & SANTESSON 1942) and histologic studies of preoperatively radiated rectum carcinomas in man (HULTBORN 1954) have all been performed. Investigations have also revealed that by increasing distance from a well oxygenated stroma the cells in a tumour become 'protected' from the effect of ionizing radiation. Clinical quantitative measurements of oxygen tension in different parts of superficial tumours (CATER et coll. 1957, 1958, 1960) have disclosed the differences that may exist. The principle that increased O_2 tension bears a direct relationship to increased cell damage from irradiation has in the past ten years been applied in radiotherapy.

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Fig 1 Case 1 Squamous cell carcinoma of right upper lobe blocking of the right pulmonary artery with contrast injection distal to the closure Th tumour was constricting the central part of the upper lobe artery and displacing branches of the pulmonary artery

(NORDENSTROM 1962) The balloon catheter is provided with two canals one for the inflation of the balloon and one with the opening distal to the balloon for the sampling of blood from the occluded pulmonary artery The balloon catheters are introduced via the femoral vein of one side and advanced under fluoroscopy to the pulmonary artery The pulmonary arterial branch is then blocked by the injection of Urografin 30 % into the catheter balloon A small amount of contrast medium is injected through the other catheter canal, on the completion of the experiment, in order to check the effectiveness of the closure and the extent of the occluded region (Fig 1)

For obtaining the blood samples one catheter is introduced into a peripheral vein and one into the femoral artery and advanced to the lower part of the abdominal aorta

cervical carcinomas (CATER et coll., KOLSTAD 1963, EVANS & NAYLOR 1963) have made it possible to show that the oxygen tension increases in the tumour tissue during the inhalation of pure oxygen gas. No determinations of the oxygen tension in carcinoma of the lungs appear to have been published, however.

The frequently hypoxic region in the interior of a tumour implies a radiologic protection for the tumour cells. Thus in many cases the inhalation of oxygen may be calculated to give rise to increased oxygen tension only in the peripheral parts of the tumour and in the normal tissue surrounding the latter. In order, if possible, to attain a higher oxygen tension in the interior of the tumour, radiotherapy with the administration of oxygen under high pressure has been tried (CHURCHILL DAVIDSON et coll. 1955, EMERY, LUCAS & WILLIAMS 1960).

An investigation of the different possibilities of changing the oxygen milieu in different organs or tumour tissues would thus appear to be justified. A further study in more detail of some of the preliminary observations made in connection with our first attempts at balloon catheter occlusion of a pulmonary artery in man (CARLENS, HANSON & NORDENSTROM 1951) has therefore been made. The very first experiments revealed, both in dog and in man, that the blood distal to an occluded pulmonary artery is very rapidly converted from venous to arterial blood. It also has proved possible to elucidate the mechanism for this experimentally (NORDENSTROM 1954). A marked fall in blood pressure occurs distally to the occluded pulmonary artery, an increased amount of blood then passes via the bronchopulmonary vascular communications from the aorta to the pulmonary artery distal to the occlusion. The supply of venous blood is not renewed owing to the blockage of the pulmonary artery but, on the other hand, the supply of oxygenated blood via the bronchial arteries is continuous. Apart from this factor it is probable that also a certain degree of oxygenation of the blood in the occluded lung occurs due to displacement of blood in the lung by the respiratory movements.

It is the aim of the present paper to elucidate the extent to which oxygen saturation and oxygen tension can be affected (1) by closure of the pulmonary artery alone, (2) by occlusion of the pulmonary artery with simultaneous oxygen ventilation, and (3) only by oxygen ventilation.

The investigations have been carried out in four patients in connection with the preoperative investigation of bronchial carcinoma.

Methods

1. The occlusion of the pulmonary artery has been performed with the help of an earlier described method for percutaneous balloon catheterization

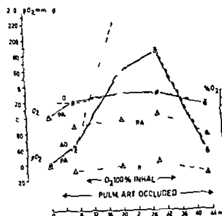


Fig 2 Blood gas values from Case 1 On closure of the pulmonary artery the oxygen saturation and tension distal to the closure increased oxygen respiration produced a considerable further rise in these values When suspending oxygen inhalation the oxygen saturation and tension in the pulmonary artery sank immediately despite continued occlusion of the pulmonary artery

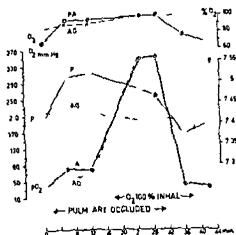


Fig 3 Case 2 A distinct increase in the pH value of the blood distal to the closure has occurred apart from the increase in the oxygen saturation and oxygen tension distal to the blocked pulmonary artery before and during oxygen breathing

AO = aorta
PA = pulmonary artery
RA = right atrium

discontinued however both the oxygen tension and the oxygen saturation seemed to sink to lower values than those obtained on analysis of the samples taken before the oxygen respiration

Case 2 Male aged 69 with tickly cough for a month before admission Roentgen examination revealed a homogeneous induration the size of a large walnut in the lower lobe of the right lung Transthoracic needle biopsy revealed this to consist of highly differentiated squamous cell carcinoma Lung function tests gave the following values FRC/TLC 50 RC/TLC 40 $FEV_{1.0}$ /VC % 65 and MVV l/min 65 Blood pressure 145/95

The analytical values are given in Fig 3 As in the first case the oxygen tension in the pulmonary artery was raised distal to the occlusion after which the tension rose further during inhalation of pure oxygen In this case the closure of the pulmonary artery was suspended before discontinuation of the oxygen respiration it is evident that then the oxygen tension in the blood of the pulmonary artery fell rapidly The oxygen tension in the aorta increased in connection with oxygen ventilation and sank to the original level when the oxygen ventilation was discontinued With closure of the pulmonary artery the oxygen saturation in the blood distal to the closure increased and was thereafter appreciably augmented during the oxygen ventilation The oxygen saturation then amounted to practically 100 both in the pulmonary artery and in the aorta in the latter the oxygen saturation decreased on suspension of closure and still further when the oxygen respiration was discontinued Analyses of the pH value of the blood were also carried out in this experiment It may be observed that there was a

2 Blood samples for the determination of oxygen saturation, oxygen tension, and in certain cases the pH of the blood, are taken practically simultaneously through the vein and artery catheters and the balloon catheter canal opening in the pulmonary artery distal to the closure Blood samples are always obtained before closure of the pulmonary artery, during a period of 10 to 15 minutes while the pulmonary is still closed, and after closure of the artery Samples are then taken during closure of the artery for 10 to 15 minutes under 100 % oxygen ventilation with a so called demander mask Occlusion of the pulmonary artery is then suspended, during continued oxygen respiration with the mask, and with continued sampling throughout this period, and, finally, during the period after termination of the breathing of oxygen

3 The pH and standard bicarbonate and carbon dioxide tensions are determined by Astrup's method The absolute error of measurement with this method amounts to ± 0 005 for pH values and to ± 1 5 mm Hg for pCO_2 determinations

The oxygen tension is determined with a modified Clark electrode ('Radiometer', Copenhagen) which in double determination gives an error of 2 % of the value read The oxygen saturation is calculated from the dissociation curve for oxyhemoglobin from the oxygen tension values obtained, and with correction for pH and temperature All the values given for the blood gases are at 37° C

Case reports

Case 1 Male aged 67 with rather severe bronchial asthma of some years duration and with cough and blood stained sputum for 6 to 7 months before admission Blood pressure 145/60 Lung function test with values corresponding to those found in cases of marked obstructive emphysema FRC/TLC 70 RV/TLC 52 $FEV_{1\,0}$ /VC % 26 and MVV_{40} l/min 26

Roentgen examination revealed a heart of normal size and in the upper lobe of the right lung a large rounded tumour 6 cm in diameter with a large central area of necrosis Transthoracic needle biopsy of the pulmonary infiltration gave material with groups of cells of highly differentiated squamous cell carcinoma

As may be seen from Fig 1 the branches of the pulmonary artery that surround the tumour have been displaced when contrast medium was injected distal to the occluded pulmonary artery The first part of the upper lobe artery was also constricted

The analytical values indicate a distinct increase in oxygen tension in the pulmonary artery distal to its closure (Fig 2) The oxygen tension in the pulmonary artery increased further when the patient breathed pure oxygen but sank rapidly when the oxygen respiration was discontinued while the pulmonary artery was kept closed

The oxygen tension in blood taken from the aorta also increased markedly during oxygen ventilation The oxygen saturation both in blood from the aorta and in blood from the pulmonary artery distal to the occlusion increased during closure and oxygen ventilation and amounted at both sites of sampling to almost 100 % As soon as the oxygen respiration was

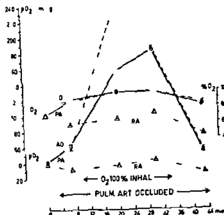


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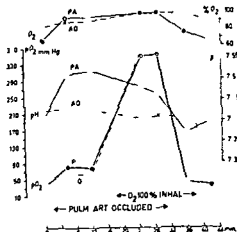


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Case reports

Case 1 Male aged 67 with rather severe bronchial asthma of some years duration and with cough and blood stained sputum for 6 to 7 months before admission Blood pressure 145/60 Lung function test with values corresponding to those found in cases of marked obstructive emphysema FRC/TLC 70 RV/TLC 52 $FEV_{1\,0}$ /VC % 26 and MVV_4 l/min 26

Roentgen examination revealed a heart of normal size and in the upper lobe of the right lung a large rounded tumour 6 cm in diameter with a large central area of necrosis Transthoracic needle biopsy of the pulmonary infiltration gave material with groups of cells of highly differentiated squamous cell carcinoma

As may be seen from Fig 1 the branches of the pulmonary artery that surround the tumour have been displaced when contrast medium was injected distal to the occluded pulmonary artery The first part of the upper lobe artery was also constricted

The analytical values indicate a distinct increase in oxygen tension in the pulmonary artery distal to its closure (Fig 2) The oxygen tension in the pulmonary artery increased further when the patient breathed pure oxygen but sank rapidly when the oxygen respiration was discontinued while the pulmonary artery was kept closed

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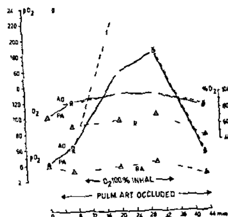


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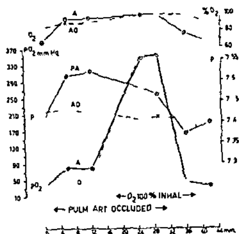


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The analytical values are given in Fig 3 As in the first case the oxygen tension in the pulmonary artery was raised distal to the occlusion after which the tension rose further during inhalation of pure oxygen In this case the closure of the pulmonary artery was suspended before discontinuation of the oxygen respiration it is evident that then the oxygen tension in the blood of the pulmonary artery fell rapidly The oxygen tension in the aorta increased in connection with oxygen ventilation and sank to the original level when the oxygen ventilation was discontinued With closure of the pulmonary artery the oxygen saturation in the blood distal to the closure increased and was thereafter appreciably augmented during the oxygen ventilation The oxygen saturation then amounted to practically 100 % both in the pulmonary artery and in the aorta in the latter the oxygen saturation decreased on suspension of closure and still further when the oxygen respiration was discontinued Analyses of the pH value of the blood were also carried out in this experiment It may be observed that there was a

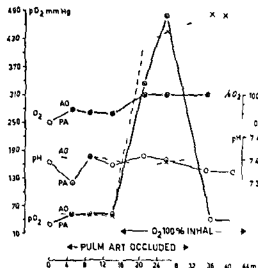


Fig 4 (above) Case 3 Marked increase in oxygen saturation and oxygen tension distal to the closed pulmonary artery during oxygen respiration no marked change in pH value of blood in pulmonary artery or the aortic blood

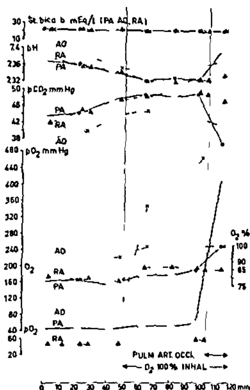


Fig 5 (right) Case 4 Only when the pulmonary artery was blocked did the oxygen tension distal to the blocking rise The pH value of the blood sank at the same time as the pCO_2 rose during oxygen respiration At closure of pulmonary artery the pH value in the pulmonary artery rose considerably as the pCO_2 sank

remarkable rise in the pH value of the blood in the pulmonary artery distal to the closure with return to values somewhat lower than the initial value after suspension of the occlusion The pH value in the aortic blood on the other hand presented no great changes during the experiment

Case 3 Male aged 72 who for several years had suffered from dyspnea and for 2 months from diabetes mellitus which had been kept under control with tolbutamide 4 months before admission he had been subfebrile and suffering from tickly cough without expectoration considerable adipositas Blood pressure 160/90 Lung function tests gave values corresponding to those found in emphysema with FRC/TLC 69 RV/TLC 49 FEV$_{1.0}$ /VC % 38 and MVV l/min 43

Roentgen examination revealed slight enlargement of the heart (total volume 1 030 ml 515 ml/m^2 body surface) and a homogeneous irregularly delimited induration the size of a plum in the anterior segment of the right upper lobe Transthoracic needle biopsy of the pulmonary induration gave tissue material with cell formation of slightly differentiated squamous cell carcinoma

The values of the pH determinations and the blood gas analyses in the pulmonary artery and aorta are recorded in Fig 4a As in the two preceding cases an increase of the oxygen tension in the pulmonary artery distal to the closure and a striking increase of the tension during 100 % oxygen ventilation with continuous blocking of the artery are evident When

with continued oxygen ventilation the closure of the pulmonary artery was suspended the oxygen tension in the blood of the pulmonary artery fell rapidly The oxygen saturation increased in the pulmonary artery during closure and still further during oxygen respiration in the same way as in the two preceding cases No definite effect either upon the pH values of the pulmonary artery or upon those of the aorta was observable neither in connection with the closure of the pulmonary artery nor with the oxygen respiration

Case 4 Male aged 63 without chest symptoms admitted to hospital on account of loss of weight general condition normal Blood pressure 145/90 Normal heart findings Roentgen examination of skeleton oesophagus stomach and colon revealed no changes but adjacent to the left pulmonary hilum a rounded induration was totally blocking the upper lobe bronchus Bronchoscopic biopsy disclosed an undifferentiated small-cell carcinoma (oat-cell carcinoma) Spirometric examination produced moderately increased quotients FRC/TLC 64 and RV/TLC 42 and rather normal flows $FEV_{1.0}$ /VC % 63 and MVV l/min 75

The oxygen ventilation in this experiment was not begun until after the lapse of about 50 minutes (Fig 5) The values for oxygen saturation and oxygen tension were fairly constant during the period before the oxygen ventilation During the ventilation however the oxygen tension in the aorta as in the preceding experiments rose considerably while the venous blood in the right atrium and the pulmonary artery was not definitely changed The oxygen saturation rose somewhat both in the venous and in the arterial blood during the oxygen respiration which was continued until the conclusion of the experiment After about 50 minutes of oxygen ventilation the left pulmonary artery was blocked whereupon the oxygen tension and the oxygen saturation in the pulmonary artery rose appreciably This coincides completely with the experience gained in the previous experiments

A slow increase of the pCO_2 values (with slow depression of the pH values) was present also in this case during the period immediately preceding the oxygen respiration and during the first part of the oxygen respiration On closing of the left pulmonary artery the pCO_2 value sank markedly (with a rise in the pH value) in the blood to the occluded lung which much resembles the changes observable in the pH values in Case 2 (Fig 3)

Discussion

A consistent feature in these investigations was a slight increase in the oxygen tension distal to the occluded pulmonary artery The very marked increase in oxygen tension in the pulmonary artery distal to the closure however occurred during simultaneous respiration with pure oxygen Both the oxygen saturation and the oxygen tension in the pulmonary artery then on an average attained the same values as corresponding values for the arterial blood This implies that the arteries, capillaries and veins of the occluded lung should contain 100 % oxygenated blood The only unsaturated supply of blood that can conceivably lower the oxygen content in the lung must come from the bronchial veins This of course does not necessarily mean that a high oxygen content can be produced in this way also in the central parts of pulmonary tumours The speed with which the diffusion of oxygen gas from the surroundings of the tumour to its interior can eventually be increased in the manner described

cannot yet be assessed. Direct measurements of tension in the centre of the tumour would be necessary for this to be achieved.

The rise in the pH value of the blood observed in Cases 3 and 5 appears to be connected directly with the closure of the pulmonary artery.

SUMMARY

The possibilities of changing the oxygen milieu in a lung distal to an occluded pulmonary artery during oxygen respiration have been investigated in four cases of pulmonary carcinoma. A considerable rise in the pH value of the blood in the occluded lung was observed in two of the cases.

ZUSAMMENFASSUNG

Es wurde untersucht, inwieweit man in 4 Fällen von Lungenkarzinom das Sauerstoffmilieu der Lunge distal von einer verschlossenen Pulmonalarterie durch Sauerstoffeinatmung beeinflussen konnte. Eine beträchtliche Erhöhung der pH Koncentration in der verschlossenen Lunge konnte in zwei Fällen festgestellt werden.

RÉSUMÉ

Les auteurs ont étudié dans quatre cas de cancer du poumon les possibilités de modifier la teneur en oxygène dans un poumon en aval d'une occlusion d'une artère pulmonaire au cours de l'inhalation d'oxygène. Ils ont observé dans deux cas une élévation considérable du pH du sang dans le poumon occlus.

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FROM THE DEPARTMENT OF PATHOLOGY II, UNIVERSITY OF UMEÅ, AND THE GUSTAF WERNER INSTITUTE, UNIVERSITY OF UPPSALA, SWEDEN

MICROANGIOGRAPHIC STUDIES ON CHANGES IN THE CEREBRAL VESSELS AFTER IRRADIATION

II Proton beam lesions in the rat

by

O HASSLER

The aim of the present study was largely the same as that set for the first work of this series (HASSLER & MOVIN 1966) The experimental conditions in the latter resembled those existing when moderate 'therapeutic' radiation doses over large radiation fields are delivered in the usual therapy of malignant tumours The experimental conditions in the present study were arranged to resemble those when high doses (necrose doses) of radiation are administered to destroy small limited areas of the brain, e g in stereotaxic irradiation

Material and Methods Twenty six albino rats of the Wistar strain were used, these were of both sexes and weighed 200 to 300 g at irradiation The animals were marked in the external ears and were not kept in individual cages The sexes were not mixed within the cages The animals were fed rat chow with water ad lib

Irradiation technique The irradiations were performed with a 185 MeV proton beam of circular, 3 mm wide cross section, from a 230 cm synchrocyclotron The irradiation technique was exactly the same as that used by LARSSON (1960)

Submitted for publication 8 September 1965

Table

Survey of the proton irradiated rat material

Rat No.	Dose (rad)	Time betw irrad and death (days)	Investigation	Haemorrhages*	Necrosis**	Telangiectases **
1	20 000	10	Microradiogr	—	—	—
2	20 000	15	Peroxidase	+	+	—
3	20 000	15	Microradiogr	+	+	—
4	20 000	15	Peroxidase	+	++	—
5	20 000	30	»	+	+++	—
6	20 000	30	Microradiogr	+	++	—
7	20 000	30	Peroxidase	+	+++	—
8	20 000	90	Microradiogr	+	+++	+
9	20 000	90	Peroxidase	++	+++	++
10	20 000	90	»	+	+++	+
11	20 000	143	»	++	+++	+
12	20 000	180	Microradiogr	++	+++	+++
13	20 000	180	Peroxidase	+	+++	++
14	20 000	180	»	+	+++	+++
15	20 000	238	»	+	+++	+++
16	20 000	270		+	+++	+++
17	20 000	270	Microradiogr	+	+++	+++
18	[illegible]600	270	Peroxidase	+	+++	+
19	20 000	360	»	+	+++	++
20	20 000	360	»	+	+++	++
21	20 000	360	»	+	+++	+
22	10 000	360	Microradiogr	+	+++	+
23	10 000	360	»	+	+++	+
24	40 000	30	Peroxidase	+	+++	+
25	40 000	30	»	+	+++	—
26	40 000	30	Microradiogr	+	+++	+

* Degree of haemorrhages was classified in the following way
- +++ Total volume of macroscopically visible haemorrhages > 1 mm
- ++ Total volume of macroscopically visible haemorrhages < 1 mm³ and/or brownish haemosiderin pigment
- + Haemorrhages only visible microscopically

** Degree of necrosis was classified in the following way
- +++ Total volume of necrotic cysts > 1 mm³
- ++ Total volume of necrotic cysts < 1 mm or a shrunken macroscopical appearance
- + Necrotic changes visible only microscopically

** Degree of telangiectases was classed into
- +++ Total length of the telangiectases in one brain > 1 mm
- ++ Total length of the telangiectases in one brain 0 1—1 mm
- + Total length of the telangiectases < 0 1 mm

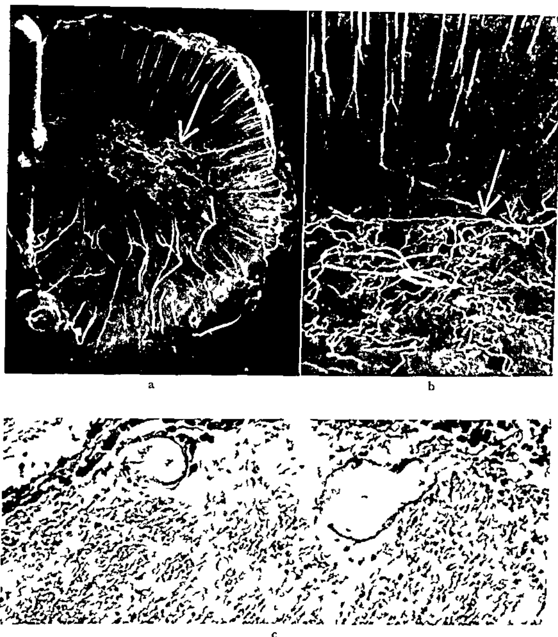


Fig 1 a) Rat 12 Microangiogram from a 1 mm coronal slice of the brain at margin of the radio necrosis Telangiectases (arrow) × 9 b) Detail of (a) Telangiectases (arrow) × 24 c) Histologic section through the same slice Two telangiectases with thin walls that consist only of endothelium and hyalinized fibrous collagen Elastin van Gieson s stain × 120

Microangiographic and histologic techniques These were exactly the same as in the preceding work of the series Haemorrhages, necrosis and telangiectases were also classified in the same way (cf Table)

Results

Gross observations All animals except two (Nos 11 and 15 in the Table) which died spontaneously, gained moderately in weight Rats 11 and 15 weighed 40 and 70 g less than at the irradiation when they died after profuse diarrhoea The brains of these two animals were fixed three hours post mortem and could be examined with the peroxidase method The general gross findings at the sites of irradiation were the same as those observed by LEKSELL et coll (1960)

Microangiography Radionecrosis was evident at 15 days (see Table) The first telangiectases appeared at 30 days and developed to a maximum at 180 days or more after irradiation (Figs 1 and 2) No telangiectases occurred in 7 rats with early radionecrosis but no rat *with telangiectases escaped necrosis* Small petechial haemorrhages were observed both early and late after the irradiation (see Table) but were not more marked than in the previous study The findings in rats 11 and 15 did not diverge markedly from those of the other animals In the irradiated areas but not in the other parts of the brains slight perivascular extravasation of the roentgen contrast medium occurred in several animals especially in those killed 10 to 30 days after irradiation

Histology The routine histologic observations were the same as those of REXED et coll (1960) The walls of the telangiectases were extremely thin and consisted only of a thin layer of endothelium and solitary hyalinized fibers of collagenous connective tissue Elastic tissue and smooth muscle were absent (Fig 1)

Discussion

Considering the well known differences between the high dose irradiation used in the present work and the low dose irradiation *employed in the preceding* work it is hardly surprising that the radionecrosis and telangiectases appeared earlier in the present study than in the other

The most interesting finding in the present work was that the radionecrosis seemed to precede the telangiectases because 7 animals killed 15 to 90 days after irradiation had *radionecrosis* with no telangiectases and no animal had telangiectases without coexisting necrosis This tendency could previously not be clearly observed because 2 animals had necrosis but no telangiectases and another 4 animals had telangiectases but no necrosis (In the last mentioned four animals, distinct parenchymatous changes could however be discerned These consisted of oedematous separation of the parenchyma and loss of solitary nerve cells and gliosis) The difference in results between the preceding and

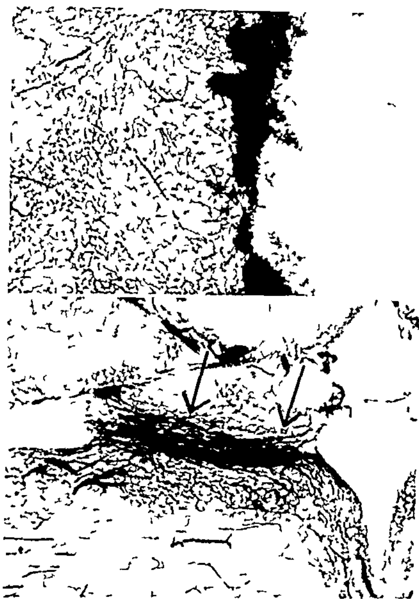


Fig 2 Peroxidase stained 0 3 mm frozen sections to demonstrate capillary angioarchitecture *Upper* Rat 7 *Radionecrosis to the right with* normal angioarchitecture and no telangiectases to the left The dark mass in the border zone is blood × 50 *Lower* Rat 16 The telangiectases (arrows) are arranged longitudinally along the direction of the beam × 50

present studies may be due to the difference in radiation dose A high dose of radiation may accelerate the development of necrosis more rapidly than that of telangiectases The results from both studies seem to indicate that it is improbable that the telangiectases precede or cause the necrosis but it may

be that telangiectases arise from radionecrosis or radiation induced parenchymatous changes

Other kinds of vascular changes, i e small petechial haemorrhages swelling of the endothelial cells, fibrinoid necrosis hyalinization and fibrosis of the vascular walls occurred mainly in connection with radionecrosis in both studies These changes were observed only in the histologic sections and never in the microangiograms, when they had been identified in the histologic sections no changes in lumen or other divergencies in structure could be discovered in the microangiograms It therefore seems probable that these vascular changes had not much influenced the circulation On the other hand they may have been associated with a pathologic permeability of the vascular walls because a slight leakage of roentgen contrast medium was often observed in close connection with them although not in the non irradiated parenchyma As has been shown in a previous work (HASSLER 1964) such a leakage may be a sign of increased vascular permeability which has also already been observed in pre necrotic stages of proton beam lesions by other methods (LARSSON 1960)

The conclusion is that some kinds of vascular changes especially increased permeability of the vascular walls and small petechial haemorrhages may be primary to the radiation necrosis Telangiectases appear later than certain parenchymatous changes and are probably secondary to them

Acknowledgements

The author is indebted to Assoc Prof B Larsson who kindly performed the irradiations of the animals The work was supported by the Swedish Medical Research Council and the U S A F School of Aerospace Medicine under contract No A F 61 (052)—740 through the European Office of Aerospace Research (O A R) United States Air Force

SUMMARY

Twenty six rats received a high but localized dose of proton irradiation to the brain and were examined 10 to 360 days later by microangiography Necrosis occurred 15 days or more after irradiation and was accompanied by increased vascular permeability Telangiectases were observed later being found in all animals killed 90 days or more after irradiation

ZUSAMMENFASSUNG

Sechsundzwanzig Ratten erhielten im Gehirn eine hohe Dose Protonenstrahlen und wurden nach 10 bis 360 Tagen mikroangiographisch untersucht. Strahlennekrosen wurden nach 15 oder mehr Tagen nach der Bestrahlung festgestellt und traten gleichzeitig mit erhohter Gefasspermeabilitat auf Teleangiektasien welche bei allen Tieren auftraten die 90 oder mehr Tagen nach der Bestrahlung getotet wurden wurden spater beobachtet

RÉSUMÉ

Vingt six rats ont reçu sur le cerveau une irradiation par des protons forte mais localisée l examen microangiographique a été fait de 10 à 360 jours plus tard La nécrose se produit 15 jours ou plus après l irradiation et s accompagne d une augmentation de la perméabilité vasculaire Plus tard on a observé des télangiectasies qui sont présentes chez tous les animaux tués 90 jours ou plus apres l irradiation

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AUS DER ABTEILUNG FUR BILDTECHNIK DER SIEMENS REINIGER WERKE AG, ER
LANGEN, DEUTSCHLAND

DREHSTROMGENERATOR UND RÖNTGEN-AUFNAHMETECHNIK

von

JOSEPH MEILER

Es mag vielleicht eine erneute Betrachtung uber den Drehstromgenerator uberflussig erscheinen da dieser seine grosse Überlegenheit uber den 2 Puls generator wohl in allen bedeutenden Rontgeninstituten Europas langst uber zeugend erwiesen hat Überraschenderweise konnte aber diese Überzeugung außerhalb Europas noch wenig Fuß fassen denn dort findet der Drehstrom Rontgengenerator immer noch nur sehr zogernd Eingang Bei der uberragen den Bedeutung die dem Drehstromprinzip fur den Rontgenbetrieb zweifellos zukommt erscheint es mir deshalb nicht nur gerechtfertigt sondern notwendig uber seine Vorzuge aufgrund neuer Messungen zu berichten

Meine fruheren einschlagigen Arbeiten (MEILER 1949 1950) berucksichtig ten die Verhaltnisse bei der damals allein angewendeten Normaltechnik und bei einer Rohre mit der seinerzeit ublichen Vorfilterung von etwa 1 2 mm Al GIW Demgegenuber erfassen die neuen Untersuchungen auch den heute interessierenden großeren Spannungsbereich bis 150 kV und zeigen die Strahlenverhaltnisse bei einer Rohrenvorfilterung von 2 mm Al GIW auf, die seit einigen Jahren zur Reduzierung der Strahlenbelastung des Patienten als Mindestwert vorgeschrieben ist

Bei der Redaktion am 23 Dezember 1964 eingegangen

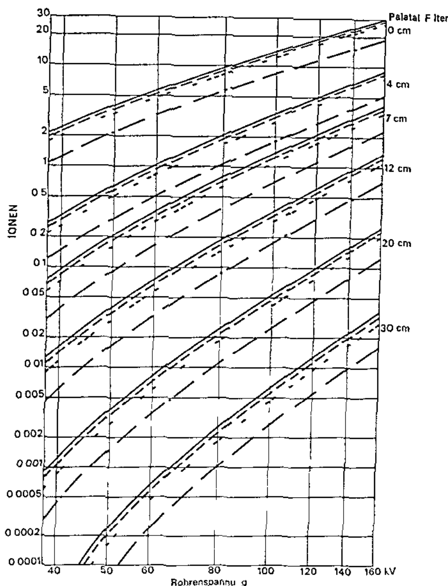


Abb 1 Ionendosis je 1 mAs in 1 m FA hinter verschiedenen Palatalfiltern als f (kV) — bei reiner Gleichspannung — — — bei 12 Pulsbetrieb bei 6 Pulsbetrieb — — bei 2 Pulsbetrieb (Eigenfilterung der Rontgenrohre 2 mm Al GlW)

1 *Meßanordnung*

Die Messungen wurden an einem 12 Pulsgenerator Tridoros 4 mit dem 40 kW-Brennfleck einer Bianguli Rohre Bi 150/30/40 (Vorfilterung 2 mm Al GlW) ausgefuhrt Die Rontgenstrahlen Dosis wurde mit einem EIL-Dosimeter mit kleiner Meßkammer bei einem Fokus Kammer Abstand von 1 m gemessen Als Filter wurden Platten aus Kunststoff Palatal P F (spez

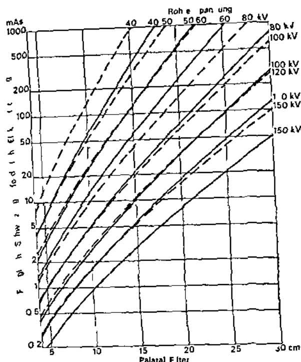


Abb. 2. Zur Erzielung gleicher Schwärzung (S = 0,9) bei Verwendung einer Universalfolie erforderliche mAs-Werte in Abhängigkeit von der Filterstärke für verschiedene Röhrenspannungen. — bei 12-Pulsbetrieb, — — — bei 2-Pulsbetrieb

Gewicht = 1,2) verwendet, der in seinen Absorptions- und Streuverhaltnissen den medizinischen Objekten nahekommt. Die Filterplatten wurden röhrennah angeordnet. Zudem wurde das ausgeblendete Strahlenfeld nur wenig größer gewählt als die Meßkammer. So blieb die Streustrahlung am Meßort unbedeutend.

Die Messungen beim 12-Pulsbetrieb wurden mit 150 mA Röhrenstrom und variabler Zeit vorgenommen und der jeweilige mAs-Wert mitgemessen. Durch Reduzierung des Röhrenstromes auf 1 mA ließ die Röhrenspannung infolge der Glättung durch die Kabelkapazität (12 m einfache Kabellänge) keine Pulsationen mehr erkennen, so daß in dieser Weise auch die Messungen bei reiner Gleichspannung an der gleichen Anlage ausgeführt werden konnten. Durch Abtrennen einer Phase des Drehstroms konnten am gleichen Generator und mit der gleichen Röhre ferner die Verhältnisse für den 2-Pulsbetrieb bei 100 mA Röhrenstrom untersucht werden.

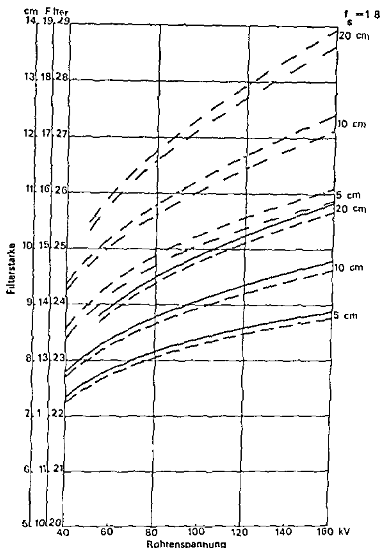


Abb 3 Zunahme des im Schwarzungsbereich 0 4 1 8 dargestellten Objektumfanges mit der Rohrenspannung bei Abbildung der Filterwerte 5 bzw 10 und 20 cm Talatal mit der Schwarzung 1 8 fur die Gradationen γ = 2 und 3 — 12 Pulsbetrieb γ = 3 — — 12 Pulsbetrieb γ = 2 — — — 2 Pulsbetrieb γ = 3 — - 2 Pulsbetrieb γ = 2

2 *Die Rontgenstrahlen Ergiebigkeit*

Die erzielten Dosismeßwerte wurden durchweg auf 1 mAs umgerechnet Die Ergebnisse liefern die Kurven der Abb 1 die die Ionen Dosis in Abhangigkeit von der Rohrenspannung fur verschiedene Filterwerte zeigt Neben den aus den jetzigen Messungen erhaltenen Kurven fur reine Gleichspannung, 12 Puls- und 2 Pulsbetrieb wurden auch die Kurven fur den 6 Pulsgenerator eingezeichnet, die aus vielen fruheren Vergleichsmessungen sich ergaben

Aus dieser Gegenüberstellung ersieht man, daß für die praktisch interessierenden Filterungen bei gleicher Scheitelspannung und gleicher mAs-Menge der 6-Pulsgenerator im Mittel das 1,6fache, der 12-Pulsbetrieb ca. das 1,85fache und die vollkommen konstante Gleichspannung als Idealfall ungefähr das 2fache an Dosis liefern wie der 2-Pulsbetrieb. Die Unterschiede sind größer bei niedrigeren Spannungen und stärkeren Filterungen, geringer bei hoher Röhrenspannung und bei schwächeren Filtern.

3. *Der mAs-Bedarf für gleichgeschwärzte Aufnahmen*

Im weiteren wurden die mAs-Mengen ermittelt, die bei Verwendung einer Verstärkerfolie zur Erzielung gleicher Filmschwärzungen benötigt werden. Bei diesen Untersuchungen habe ich nur den 12-Puls- und den 2-Pulsgenerator berücksichtigt. Für den 6-Pulsbetrieb und die reine Gleichspannung lassen sich die entsprechenden Werte aus den Dosiskurven der Abb. 1 hinreichend genau abschätzen. Ebenso genügt es, diese Untersuchungen auf die Universal-folie zu beschränken, da die Verhältniswerte des mAs-Bedarfs bei unterschiedlichen Betriebsarten, auf die es bei dem vorgesehenen Vergleich vor allem ankommt, bei anderen Folientypen nicht wesentlich differieren können.

Die Meßanordnung war die gleiche wie unter 1. beschrieben, nur trat die Filmkassette an die Stelle der Dosismeßkammer. Das ausgeblendete Feld blieb klein, um die Streustrahlung auf einem vernachlässigbaren Wert zu halten. Die jeweiligen Schaltzeiten waren so gewählt, daß sie möglichst den praktischen Verhältnissen entsprachen. Überdies sind bei den heutigen Röntgenfilmen die Abweichungen vom Reziprozitätsgesetz z. T. schon vernachlässigbar, was auch bei dem hier verwendeten Film zutrifft. Auf gleiche Entwicklungsbedingungen wurde geachtet.

Es wurden zunächst für verschiedene Röhrenspannungen und Filterwerte Schwärzungskurven ($S = f$ (mAs)) aufgenommen. Diesen wurden dann die mAs-Werte entnommen, die zur Erzielung der Schwärzung $S = 0{,}9$ (mittlerer Schwärzungswert üblicher Röntgenaufnahmen) erforderlich sind. Die Ergebnisse zeigt die Abb. 2 als Funktion der Filterstärke für verschiedene Röhrenspannungen. Für den 6-Pulsbetrieb liegen die benötigten mAs-Werte im Mittel um etwa 20% höher als die des 12-Pulsbetriebes.

Die Darstellung gilt für die benutzte Film-Folienkombination und normale Entwicklungsbedingungen bei Aufnahmen ohne Streustrahlenraster sowie bei engster Ausblendung. Bei geänderten Bedingungen, z. B. anderem Folienmaterial und Verwendung eines Streustrahlenrasters sowie einem größeren Aufnahmefeld, ergeben sich andere Werte des mAs-Bedarfes. Die Relationen dieser Werte für die verschiedenen Betriebsarten bleiben jedoch annähernd die gleichen, was für unsere Betrachtungen das Wesentliche ist.

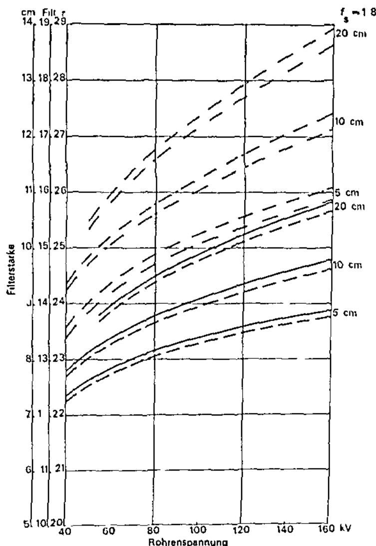


Abb. 3. Zunahme des im Schwärzungsbereich 0,4 ... 1,8 dargestellten Objektumfanges mit der Röhrenspannung bei Abbildung der Filterwerte 5 bzw. 10 und 20 cm Material mit der Schwärzung 1,8 für die Gradationen $\gamma = 2$ und 3. —— 12-Pulsbetrieb $\gamma = 3$; — — 12-Pulsbetrieb $\gamma = 2$; — — — 2-Pulsbetrieb $\gamma = 3$; — — 2-Pulsbetrieb $\gamma = 2$

2. *Die Röntgenstrahlen-Ergiebigkeit*

Die erzielten Dosismeßwerte wurden durchweg auf 1 mAs umgerechnet. Die Ergebnisse liefern die Kurven der Abb. 1, die die Ionen-Dosis in Abhängigkeit von der Röhrenspannung für verschiedene Filterwerte zeigt. Neben den aus den jetzigen Messungen erhaltenen Kurven für reine Gleichspannung, 12-Puls- und 2-Pulsbetrieb wurden auch die Kurven für den 6-Pulsgenerator eingezeichnet, die aus vielen früheren Vergleichsmessungen sich ergaben.

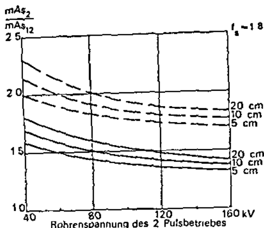


Abb 5 Verhaltnis der für gleiche Schwarzungen erforderlichen mAs Werte bei 2 Pulsbetrieb gegenuber 12 Pulsbetrieb fur drei Objektfälle — bei aquivalenten Rohrenspannungen — — — bei gleichen Scheitelspannungen

verschiedenen Details dann entsprechend geringere Kontraste so daß u U Einzelheiten die schon einen geringen Strahlungskontrast ergeben, im Bild uberhaupt nicht mehr erkennbar werden

Die Abb 3 gilt fur den Fall daß die auf den Film treffende Strahlung keine nennenswerte Streustrahlung enthalt Der im praktischen Fall jedoch oft sehr erhebliche Streustrahlenanteil kann den zur Abbildung kommenden Objektumfang u U etwas vergroßern, vermindert aber weit mehr die Bildkontraste Die dadurch bedingte Einbuße an Bildinformation moglichst zu vermeiden ist Aufgabe der Streustrahlenraster Zu einem ahnlichen Effekt wie die Streustrahlung fuhrt die Schleierbildung des Films die daher durch Verwendung guten Filmmaterials und durch einwandfreie Entwicklungsbedingungen moglichst klein gehalten werden muß

5 *Aquivalente Spannungen*

Fur die Rontgenpraxis ist das Bildergebnis entscheidend Ein korrekter Vergleich verschiedener Betriebsarten muß dieses berucksichtigen indem er von Bildern moglichst gleichen Kontrastes und gleicher Schwarzungen ausgeht Der Bildkontrast wird soweit es die Rontgenapparatur betrifft von dem Verlauf und der Hohe der Rohrenspannung bestimmt Fur gleichen Kontrast benotigt man bei stark pulsierender Spannung einen hoheren Scheitelwert als bei weniger sich andernder Spannung Fur 12 Puls und 2 Pulsbetrieb sind die aquivalenten Spannungen die den besten Kontrast angleich ergeben unmittelbar der Abb 3 zu entnehmen Es sind eben jene Spannungspaare die zur Abbildung des gleichen Objektumfanges fuhren,

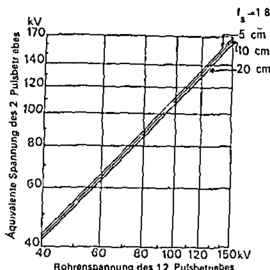


Abb. 4. Äquivalente Spannungen des 2-Pulsbetriebes als Funktion der Röhrenspannung des 12-Pulsbetriebes für drei darzustellende Filterbereiche

4. *Der zur Abbildung kommende Objektumfang*

Der im Röntgenbild darstellbare Objektumfang hängt einerseits vom Objekt selbst sowie von den Belichtungsdaten ab, die zusammen vorwiegend das *Strahlenrelief* bestimmen, andererseits von den fotografischen Gegebenheiten, insbesondere der Gradationskurve des Filmmaterials. Diese ergibt sich nicht allein aus den *Filmeigenschaften*, sondern wird auch von den Entwicklungsbedingungen beeinflußt. Je höher die Gradation (γ) ist, um so größer wird der Bildkontrast, aber um so geringer der zur Abbildung kommende Objektumfang. In der Röntgenologie wird, um das einzelne Detail mit möglichst großem Kontrast darstellen zu können, ein hoher γ-Wert bevorzugt. Er beträgt bei den heute üblichen Röntgenfilmen bei einwandfreier Entwicklung ca. 3, kann aber bei anderem Filmmaterial und ungünstigen Entwicklungsbedingungen bis auf etwa 2 absinken.

Die Abb. 3 gibt für diese beiden γ-Werte in Abhängigkeit von der Röhrenspannung die Filterwerte an, hinter welchen die Schwärzung S = 0,4 zustande kommt, wenn die Filterwerte 5 bzw. 10 oder 20 cm Palatal mit der Schwärzung S = 1,8 abgebildet werden. Dabei ist angenommen, daß in dem Bereich von S = 0,4 bis 1,8 die Schwärzungskurve geradlinig verläuft. Die Kurven lassen also aus der Differenz gegenüber 5 bzw. 10 und 20 cm Palatal den im dem Schwärzungsbereich S = 0,4 — 1,8 zur Abbildung kommenden Objektumfang erkennen. Man sieht, daß dieser nicht nur mit der *Röhrenspannung*, sondern auch erheblich mit der Stärke des Objektes zunimmt. Weniger differieren die einander entsprechenden Kurven des 12-Puls- und des 2-Pulsbetriebes. Beträchtlich beeinflußt dagegen den Bildumfang der γ-Wert. Er ist bei $\gamma = 2$ etwa um die Hälfte größer als bei $\gamma = 3$. Allerdings zeigen die

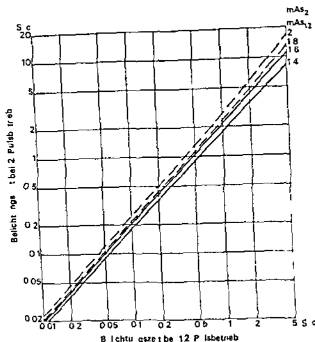


Abb 6 Kurzestmogliche Belichtungszeiten mit dem 50 kW Brennfleck beim Zweipulsbetrieb als Funktion der Belichtungszeiten beim Zwolfpulsbetrieb fur die Verhaltnisse

$\frac{mAs}{mAs}$ = 1 4 und 1 6 bei aquivalenten Spannungen (—)

$\frac{mAs}{mAs}$ = 1 8 und 2 bei gleichen Scheitelspannungen (— —)

Ausnutzung der gesamten Brennfleckbahn der Drehanodenrohre infolge der großen Konstanz der Rohrenspannung zustande

Wie Untersuchungen uber die Unscharfeverhaltnisse bei Lungenaufnahmen aufgezeigt haben die ich (MEILER 1963) im Anschluß an die Arbeiten von BERGER (1961 1963) uber die im Thorax Raum auftretenden Objektgeschwindigkeiten durchgefuhrt habe sind hier zur Vermeidung storender Bewegungsunscharfen bereits die kurzesten Zeiten erforderlich, die mit dem Drehstromgenerator erreichbar sind Eine Verdoppelung dieser Zeiten laßt ohne Zweifel die schnell bewegten Partien nicht mehr richtig zur Darstellung bringen Ahnliches gilt fur Magenaufnahmen Aber auch bei der Untersuchung von Organen ohne Eigenbewegung kann sich eine so erhebliche Verlangerung der Belichtungszeit nachteilig auswirken, vor allem, wenn der Allgemeinzustand des Patienten ein Stillhalten wahrend der Aufnahme nicht

bei denen also jeweils das gleiche Filterpaar mit demselben Kontrast (S = 0,4 und 1,8) dargestellt wird.

Die Abb. 4 zeigt diese äquivalenten Spannungen des 2-Pulsbetriebes als Funktion der 12-Pulsspannung für die drei untersuchten Objektfälle. Die äquivalenten Spannungen ergeben für jeweils zwei Filterwerte exakt den gleichen Kontrast. Es läßt sich aber zeigen, daß dann auch für den übrigen abgebildeten Filterbereich selbst in ungünstigen Fällen, d. h. bei niedrigen Spannungen und schwachen Objekten, praktisch keine feststellbaren Kontrastunterschiede verbleiben.

6. *Das Verhältnis des mAs-Bedarfes*

Für unsere Betrachtungen interessiert nun weiter das Verhältnis der mAs-Werte, die bei äquivalenten Spannungen zu gleichen Schwärzungen führen. Wir ermitteln es aus den Kurven der Abb. 2. Das Ergebnis stellt die Abb. 5 dar. Sie zeigt als Funktion der Röhrenspannung des 2-Pulsbetriebes für die drei untersuchten Objektfälle, um wieviel höher der mAs-Bedarf beim 2-Pulsgenerator gegenüber dem 12-Pulsbetrieb ist.

Unter den in der Praxis in Betracht kommenden Bedingungen für Röhrenspannung und Filterung beansprucht der 2-Pulsbetrieb für kontrastgleiche Aufnahmen etwa das 1,4 ... 1,6fache an mAs wie der 12-Pulsgenerator. Der Unterschied ist größer bei niedrigen Röhrenspannungen sowie stärkeren Filterungen und umgekehrt.

7. *Das Verhältnis der Belichtungszeiten*

Bei der Aufnahme von bewegten Objekten strebt man zur Ausschaltung einer störenden Bewegungsunschärfe möglichst kurze Belichtungszeiten an. Daher haben die bei den verschiedenen Betriebsarten erreichbaren kürzesten Aufnahmezeiten besondere Bedeutung, und wir wollen sie am leistungsfähigsten heute verwendeten Brennfleck — an dem für 50 kW — untersuchen. Zu diesem Zweck ermitteln wir die Zeiten, mit denen dieser Fokus bei Ausnutzung der jeweils zulässigen höchsten Leistung die bei äquivalenten Spannungen erforderlichen mAs-Werte schalten läßt.

Die voll ausgezogenen Kurven der Abb. 6 zeigen diese kürzest möglichen Zeiten für den 2-Pulsbetrieb als Funktion der beim 12-Pulsgenerator erreichbaren Zeiten für die mAs-Verhältnisse $mAs_2 : mAs_1 = 1,4$ und 1,6.

Daraus ist zu ersehen, daß der 2-Pulsbetrieb für äquivalente Aufnahmen und bei gleicher Ausnutzung der zulässigen Röhrenlast durchweg das 1,7 ... 2fache an Belichtungszeit erfordert wie der 12-Pulsgenerator. Der Gewinn an Zeit beim letzteren kommt durch die hohe Dosisausbeute und die gleichmäßige

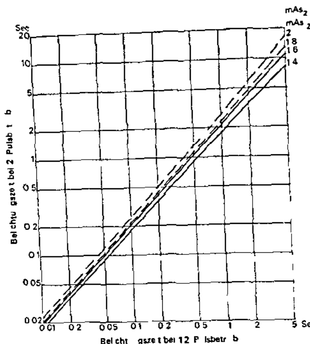


Abb 6 Kurz estmogliche Bel chtungszeiten mit dem 50 kW B ennfleck be m *Zweipulsbetrieb als Funktion der Belichtungs* zeiten beim Zwolfpulsbetrieb fur d e Verhaltnisse

$\frac{mAs}{mAs}$ = 1 4 und 1 6 bei aquivalenten Spannungen (—)

$\frac{mAs}{mAs_1}$ = 1 8 und 2 bei gleichen Sche telspannungen (— —)

Ausnutzung der gesamten Brennfleckbahn der Drehanodenrohre infolge der großen Konstanz der Rohrenspannung zustande

Wie Untersuchungen *uber die Unscharfeverhaltnisse bei Lungenaufnahmen* aufgezeigt haben die ich (MEILER 1963) im Anschluß an die Arbeiten von BERGER (1961 1963) uber die im Thorax Raum auftretenden Objektge schwindigkeiten durchgefuhrt habe, sind hier zur Vermeidung storender Bewegungsunscharfen bereits die kurzesten Zeiten erforderlich die mit dem Drehstromgenerator erreichbar sind Eine Verdoppelung dieser Zeiten laßt ohne Zweifel die schnell bewegten Partien nicht mehr richtig zur Darstellung bringen Ahnliches gilt fur Magenaufnahmen Aber auch bei der Unter suchung von Organen ohne Eigenbewegung kann sich eine so erhebliche Verlangerung der Belichtungszeit nachteilig auswirken vor allem wenn der Allgemeinzustand des Patienten ein Stillhalten wahrend der Aufnahme nicht

zuläßt. In all diesen Fällen erweist der Drehstromgenerator in überzeugender Weise seine bedeutende Überlegenheit.

Im Zusammenhang mit der erreichbaren kürzesten Belichtungsdauer müssen aber auch noch die Netzbelastungen betrachtet werden. Die hohen Röhrenleistungen der Kurzzeitaufnahmen verursachen einen nicht unerheblichen Abfall der Netzspannung. Um ein einwandfreies Arbeiten der Röntgenapparatur zu gewährleisten, darf dieser Spannungsabfall bekanntlich nicht größer als 10 % werden. Daher können an schlechteren Netzen oft nur stark reduzierte Leistungen verwendet werden. Auch in dieser Hinsicht erweist sich der Drehstromgenerator sowohl in der 6-Puls- als auch in der 12-Puls-Ausführung als bedeutend überlegen, weil sich die gesamte Röhrenleistung auf drei Phasen verteilt und deshalb der Spannungsabfall wesentlich geringer ist als beim 2-Pulsgenerator, bei dem die Netzbelastung eine Phase allein zu tragen hat.

Beim gleichen Netzwiderstand verursacht die gleiche Röhrenleistung beim Drehstromgenerator nur einen halb so großen Spannungsabfall wie am 2-Pulsgenerator. Man kann deshalb bei Drehstrombetrieb dementsprechend stärkere Röhrenströme anwenden und auch ein schlechteres Netz noch wesentlich günstiger ausnutzen als bei 2-Pulsbetrieb. So läßt der Drehstromgenerator auch die vom Netz her gebotenen Möglichkeiten zur Erzielung kürzester Belichtungszeiten durch höchste Röhrenleistungen am besten ausschöpfen.

8. *Die Strahlenbelastung des Patienten*

Auch hinsichtlich der Strahlenbelastung des Patienten ergibt sich selbst für äquivalente Aufnahmen ein Unterschied bei den verschiedenen Generatorarten. Der Unterschied kommt in den Schichten zustande, die vor dem zur Abbildung gelangenden Körperbereich liegen, und wird um so größer, je stärker die vorgelagerte Schicht ist. Zwar werden in dem abzubildenden Bereich die Strahlungen bei äquivalenten Spannungen im gleichen Maße absorbiert, in den davorliegenden dünneren Schichten jedoch werden beim 2-Pulsgenerator zusätzlich die sehr weichen bildunwirksamen Strahlenanteile absorbiert, die bei den niedrigen Spannungskomponenten dieses Betriebes mehr entstehen als bei konstanterem Spannungsverlauf. Am stärksten trifft dieses zu für die Oberflächenschicht, durch welche die Strahlung in den Körper eintritt.

Die Strahlenbelastung ist gegeben durch die in den Körper eingestrahlte Energie abzüglich derjenigen des vom Körper durchgelassenen Primäranteiles und der aus ihm herausgestreuten Strahlung. Letztere verläßt den Körper vorwiegend auf der Eintrittsseite der Primärstrahlung. Ihr

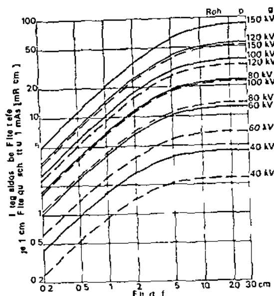


Abb 7 Das in einem prismatischen Palatalkörper von 1 cm² Querschnitt (quer zum Zentralstrahl) und x cm Länge je 1 mAs sich ergebende Dosisintegral der *Primärstrahlung* — bei 12 Pulsbetrieb — — — bei 2 Pulsbetrieb

Anteil hängt von der Größe und Form des untersuchten Körpers, von der Feldgröße und der Qualität der Primärstrahlung ab Die Zahlenangaben in der Literatur (CARLSSON 1963 KELLER 1956 SCHAAL 1963, ZIELER 1961) über diesen Anteil der je nach Fall recht erheblich sein kann, weichen zum Teil um den Faktor 2 voneinander ab was zu entsprechend unterschiedlichen Angaben über die Strahlenbelastung führt Für die Errechnung des uns interressierenden Verhältnisses der Strahlenbelastung bei den verschiedenen *Betriebsarten genügt jedoch die Berücksichtigung der Primärstrahlung* allein und die Kenntnis der Ionendosis für die in Betracht kommenden Filterstärken Wir bestimmen daher zunächst aus den Schwächungskurven (Querkurven der Abb 1) das *Dosisintegral der Primärstrahlung in einem Palatalkörper* von 1 cm² Querschnitt und *x* cm Tiefe in Richtung des Zentralstrahles eines parallelen Strahlenbündels für verschiedene Röhrenspannungen und 1 mAs Das Resultat gibt die Abb 7 als Funktion von *x* für den 2 Puls und 12 Pulsbetrieb wieder

Multiplizieren wir nun die Integralwerte die wir aus dieser Abbildung für äquivalente Spannungen der untersuchten Betriebsarten und für die zu durchdringenden Filterdicken ermitteln mit den jeweils benötigten mAs Werten dann erhalten wir mit den so errechneten Werten ein Maß für die sich entsprechenden Volumendosen Das Verhältnis dieser Werte zeigt uns das gesuchte Verhältnis der Strahlenbelastungen für äquivalente Aufnahmen

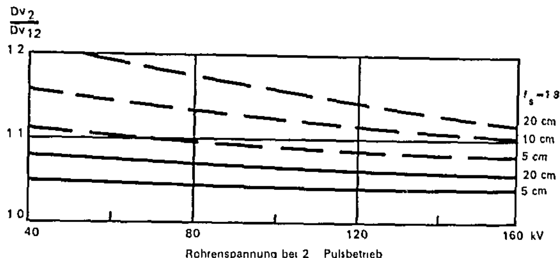


Abb. 8. Verhältnis der bei gleichen Belichtungen zustandekommenden Volumendosen bei 2-Puls- gegenüber 12-Pulsbetrieb für drei darzustellende Filterbereiche. —— bei äquivalenten Spannungen, — — — bei gleichen Scheitelspannungen.

Es ist in Abb. 8 durch die voll ausgezogenen Kurven dargestellt. Die Belastung beträgt beim 2-Pulsgenerator nur etwa 5–7 % mehr als beim Drehstromgenerator.

Häufig werden der Charakterisierung der Strahlenbelastungen die bequem zu messenden Einfalldosen zugrunde gelegt. Diese zeigen größere Unterschiede zwischen den verschiedenen Betriebsarten als die Volumendosen. Es kommen hier Verhältniswerte von etwa 1,07–1,12 zustande, die gut für die Hautbelastung zutreffen, wenngleich zu dieser auch die aus dem Körper kommende Streustrahlung wesentlich beiträgt. Sämtliche hier genannten Verhältniswerte ergeben sich bei der jetzt vorgeschriebenen Mindestvorfilterung von 2 mm Al GlW. Bei der bis vor wenigen Jahren üblichen Vorfilterung von etwa 1 mm Al GlW waren sie wie auch die absoluten Strahlenbelastungen etwas größer.

9. *Grenzverhältnisse*

Die bisherigen Ausführungen bezüglich Bildqualität, mAs-Bedarf, Belichtungszeiten und Strahlenbelastung gelten bei Zugrundelegung äquivalenter Spannungen. Nun werden sowohl die Generatoren als auch die Röntgenröhren durchweg für bestimmte Höchstspannungen ausgelegt. Das sind heute bei den leistungsfähigen Anlagen bekanntlich 125 kV oder 150 kV. In den Fällen, bei denen nun schon am Drehstromgenerator die Höchstspannungen ausgenutzt werden, wie es z. T. bei Lungen-, Magen- oder seitlichen LWS-Aufnahmen der Fall ist, können dann beim 2-Pulsgenerator die entsprechen-

den höheren äquivalenten Spannungen nicht mehr eingestellt werden, sondern nur die gleiche Maximalspannung Für die richtige Beurteilung der verschiedenen Generatorarten ist daher auch noch die Kenntnis der Verhältnisse bei gleichen Höchstspannungen wichtig

A *mAs Bedarf und abgebildeter Objektumfang* Bei gleichen Scheitelspannungen wird der dargestellte Objektumfang beim 2 Pulsbetrieb etwas geringer als beim Drehstrombetrieb, wie aus Abb 3 hervorgeht Der mAs Bedarf für gleichgeschwärzte Aufnahmen steigt auf etwa das 1,8 2fache gegenüber dem 12 Pulsbetrieb wie die gestrichelten Kurven der Abb 5 zeigen Beim 6 Pulsbetrieb wird er wiederum um etwa 20 % höher als beim 12 Pulsbetrieb

B *Belichtungszeiten* Die Zunahme des mAs Verhältnisses wirkt sich in einer weiteren etwa 30%igen Verlängerung der Belichtungszeiten aus so daß beim 2 Pulsgenerator bei gleichen Scheitelspannungen mit etwa der 2 2 2 6 fachen Aufnahmedauer gerechnet werden muß wie die gestrichelten Kurven für die mAs Verhältnisse 1 8 und 2 der Abb 6 erkennen lassen Das hat eine zusätzliche Vergrößerung der Bewegungsunschärfe und damit eine weitere Beeinträchtigung der Bildgüte zur Folge

C *Strahlenbelastung* Auch die Strahlenbelastung nimmt beim 2 Pulsbetrieb gegenüber dem Drehstrombetrieb weiter zu Die gestrichelten Kurven der Abb 8 zeigen um wieviel höher die Volumendosis bei gleichen Scheitelspannungen für gleichgeschwärzte Aufnahmen wird Die Mehrbelastung beträgt beim 2 Pulsgenerator gegenüber dem 12 Pulsgenerator

bei 125 kV bis zu etwa 14 % an Volumendosis
bei 150 kV bis zu etwa 12 % an Volumendosis
bei 125 kV bis zu etwa 22 % an Einfalldosis
bei 150 kV bis zu etwa 20 % an Einfalldosis

Die Unterschiede der Strahlenbelastung beim 6 Pulsgenerator gegenüber dem 2 Pulsbetrieb weisen annähernd dieselben Werte auf

Wir stellen also fest daß bei gleichen Scheitelspannungen die Belichtungszeiten am 12 Pulsgenerator gegenüber dem 2 Pulsbetrieb um mehr als die Hälfte beim 6 Pulsgenerator um annähernd die Hälfte gekürzt werden Dadurch können erst störende Bewegungsunschärfen vermieden und damit in jedem Falle eine einwandfreie Bildqualität erreicht werden Ferner bringt der Drehstrombetrieb ganz besonders bei den Schweraufnahmen die zu den stärksten Strahlenbelastungen führen eine nennenswerte Verminderung dieser Belastung gegenüber dem 2 Pulsgenerator So ermöglicht der Drehstromgenerator insbesondere der 12 Pulsbetrieb das beste Bildergebnis bei geringster Patientenbelastung

ZUSAMMENFASSUNG

Aus Dosis und Schwarzungsmessungen wurde ermittelt dass der Zwolfpulsbetrieb bei aquivalenten Spannungen etwa 1/3 weniger mAs und etwa die halben Belichtungszeiten, bei gleichen Scheitelspannungen dagegen bis zur Halfte der mAs und nur etwa 40 % der Zeiten benotigt wie der Zweipulsbetrieb Die Verteilung der Netzbelastung auf drei Phasen bringt beim Drehstromgenerator nur einen halb so grossen Spannungsabfall und lasst daher auch an schlechteren Netzen starkere Rohrenstrome ausnutzen

SUMMARY

It was found by dose and density measurements in a comparison between 12 pulse and 2 pulse operation that at equivalent voltages the former required about one third less mAs and about half the exposure time of the latter while at the same peak voltage the corresponding values were half as much mAs and 60 % less exposure time The voltage drop was reduced to 50 % when using the three phase generator which thus permits high tube currents to be taken from poor mains

RÉSUMÉ

Des mesures de dose et de noircissement ont montré que pour des tensions équivalentes le fonctionnement en hexaphasé permet de réduire les mAs d un tiers environ et le temps de pose de moitie environ et pour la même tension de crete il permet de réduire les mAs de moitié et le temps de pose de 60 % par rapport au fonctionnement en monophasé Avec un générateur polyphasé la répartition de la charge du secteur sur 3 phases réduit la chute de tension de moitie et permet par conséquent de disposer d intensités plus fortes dans le tube meme quand le secteur est mauvais

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— Der Wandel der Rontgenapparatur und des Rohrenspannungsverlaufes in seinen Aus wirkungen auf die Rontgenaufnahmetechnik Fortschr Rontgenstr 101 (1964) 547

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Book reviews

Reports of the United Nations Scientific Committee on the Effects of Atomic Radiation General Assembly Official Records — Seventeenth Session Supplement No 16 (A/5216) 442 pages 87 diagrams 166 tables Nineteenth Session Supplement No 14 (A/5814) 170 pages 38 diagrams 61 tables United Nations New York 1962 and 1964

Radiation protection questions have lately for obvious reasons aroused widespread interest However the general public has only vague ideas about radiation hazards some of which have often been unduly emphasized People living near nuclear energy establishments have shown excessive apprehension even though releases of activity are strictly controlled and patients have been reluctant to undergo medically desirable radiologic examinations or treatments even if carried out with due precautions regarding unnecessary radiation On the other hand important hazards which could easily be avoided have been neglected Inadequate knowledge concerning radiation protection also appears to prevail among scientists and medical specialists who have not made the subject one for special study

The present works go a long way towards presenting relevant facts and conclusions that can be based upon them They are not easily surveyable or digestible books — the subject matter is too extensive and varied for this to be possible — but they well repay close study

The first report from 1962 gives a detailed survey of the various types of natural and artificial radiation sources A large part of the book is devoted to fall-out from nuclear weapons tests and presents a wealth of data on measured activities and radiation doses (the latter often only indirectly calculated from assumed values of activity in various tissues where direct measurement is impossible) The mechanisms of fall-out distribution over the world and the passage of activity through food chains are discussed The activity and dose figures to be expected in the future are calculated under various assumptions on the extent of future weapons tests However other sources such as medical irradiation of patients are also considered and measurements from many countries are given Diagnostic radiology is found to be an important source of radiation to whole populations and means of minimizing this irradiation are discussed

Known and suspected somatic and genetic effects of radiation are then considered in an attempt to assess radiation hazards The difficulties in extrapolating from animal experiments at relatively large doses to effects of small doses in man are stressed as well as the difficulties of proving by epidemiologic methods the existence or non existence of certain radiation effects in large populations The meagre basis for many current opinions is exposed Most of the literature and many unpublished documents have been utilized Anybody seriously interested in radiation protection and having some previous knowledge of fundamental facts will find a wealth of information on which to base an opinion on pertinent questions For those not versed in modern radiobiology some fundamentals are summarized in an appendix

The last report from 1964 treats only two special subjects the contamination of the environment by nuclear explosions, and the possibility of quantitatively assessing the risk of induction of malignancies in man Only new information obtained since 1962 is discussed and the reader is referred to the 1962 report for the necessary background The first section gives a multitude of data not lending themselves to a review The important long range problem posed by long life ^{14}C in spite of low momentary dose rate may be mentioned In

the second section the dose proportionality of the incidence of some radiation effects (leukemia and other malignancies) is confirmed in the range of about 100 to 1 000 rad but it is pointed out that for small doses the incidence may be much lower than if proportionality obtained down to dose zero

Sten Benner

Recommendations of the International Commission on Radiological Protection (as amended 1959 and revised 1962) ICRP Publication 6 Pergamon Press, Oxford and New York 1964 70 pages

One purpose of this publication has been to supplement and clarify several statements of the original recommendations of 1959 that have been found to be open to misunderstanding and to give due regard to the recent publications of the ICRU A few changes in the content of the recommendations have also been made Another purpose has been to correct numerical and other errors in the commission s Publications 2 and 3 and to add fresh material to some of the tables

The present book begins with a description of the organization of the commission which is followed by the explanatory statements and amendments with comments on the reasons for them The original recommendations are then reprinted with the new material in footnotes or incorporated in the main text The supplements to Publications 2 and 3 end the book The general outlook of the commission remains unchanged and the amendments refer only to a limited number of points these are however by no means unimportant, and the additional explanations given to some unchanged paragraphs are most useful The publication may be considered indispensable to all those working in a responsible position with any type of ionizing radiation

Sten Benner

PRÉCIS DE CURIETHÉRAPIE, ENDOCURIETHÉRAPIE PLESIOCURIETHÉRAPIE Par B PIERQUIN avec la collaboration de D CHASSAGNE et R PERE 344 pages et 195 figures Masson & Cie Paris 1964

This book reviews the clinical fields of application of radioactive isotopes with special reference to the treatment of malignant tumours A short description of the discovery of the isotopes experiences from their first use in clinical practice and isotopes employed today for implantation by injection as well as for surface application are also included

The author (B PIERQUIN) in his capacity as Director of the Department of Interstitial Radiotherapy at the Gustave Roussy Institute has had wide experience in questions concerning radiation protection dosimetry and techniques for applying these isotopes These he discusses in their relation to the treatment of tumours in different locations

The most interesting sections are those on ^{192}Ir whose properties (HVT 74 days mean energy (γ) 0 3 MeV) suggest that it might be used to replace radium in clinical work The author s method of working with inactive applicators prior to dosimetry using transverse tomography and not implanting radioactive material until later deserves the closest attention This technique lessens the exposure to radiation for both patient and medical staff increases the patient s tolerance because of the thinner applicators used and widens the indications for interstitial radiotherapy

The book which is being translated into English can be warmly recommended to all interested in the field

G Notter

ACTA RADIOLOGICA

OFFICIAL ORGAN OF THE RADIOLOGICAL SOCIETIES OF
DENMARK FINLAND NORWAY AND SWEDEN

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Fasc 6 | | December

OSTEONECROSIS AND SARCOMA FOLLOWING EXTERNAL IRRADIATION OF INTRACEREBRAL TUMORS

by

N O BERG, T LANDBERG and M LINDGREN

It was long believed that osseous tissue is relatively insensitive to ionizing radiation The first case of radiation osteonecrosis was published by BAENSCH as late as 1927 since when numerous others have been reported Most of these radiation reactions have been seen in the femoral neck mandible clavicle spine ribs and pelvis KOLAR & VRABEC (1960) reported 110 personal cases Aseptic osteonecrosis of the cranium not due to malignancy appears to be rare for only some 25 cases are on record The lesion was first reported by BALLI & BARBANTI SILVA (1931) who also described its histologic appearances Further cases have been contributed by LOREY & SCHALTENBRAND (1932) CAMP & MORETON (1945) VOGT (1949) KNITTEL (1955) SALVINI (1956) KOLAR & VRABEC (1957) RUBE (1957) HAUBRICH & BREUER (1958), FREYER (1959) WACHTLER (1961) BROTSLAVSKIJ (1962) MIRIMOVA & ANDREEVA (1962) and LUGER et coll (1963)

MARIE et coll (1910) described the induction of osteosarcoma by roentgen

From the Department of Pathology (Director C G Ahlstrom) and the Department of Radiotherapy (Director M Lindgren) University Hospital Lund Sweden Submitted for publication 8 June 1965

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Present material

Osteonecrosis of the calvarium Roentgenograms of patients who had received a full course of radiation treatment during the period 1946—1958 for primary intracranial tumors were re examined, and the changes observed were correlated with other findings Roentgen examination after the conclusion of treatment had suggested osteonecrosis in 25 patients In four of them, however, the further course indicated that the lesions were of infectious origin (suppuration and migration of sutures within 3 months of completion of treatment), in two the lesions proved to be metastases from medulloblastoma (changes also in other parts of the skeleton within 11 months of the conclusion of treatment), and in one patient re examination of films taken before therapy disclosed that the changes, though then slight, had already commenced The roentgenograms in one patient revealed necrosis developing into sarcoma and in another an osteolytic sarcoma without previous necrosis

The material thus consisted of 16 patients with uncomplicated osteonecrosis and 2 patients (see below) with sarcoma

Treatment was administered with 170 kV roentgen irradiation The other radiologic data, sex distribution, age distribution, and the diagnoses for which the 16 patients were treated are given in Table 1 A Thoraeus filter (HVL = = 1 5 mm Cu) was used in two patients and a filter of 0 5 mm Cu + 1 mm Al (HVL = 0 9 mm Cu) in the remaining patients The skin doses ranged between 1 100 R and 4 500 R, the larger doses usually being delivered in several series of 2 to 4 weeks duration at intervals of 4 to 6 weeks, one treatment was given daily (except Sundays) with the irradiation of one field per treatment The intervals between the end of radiation treatment and detection

Table 1

Data concerning 16 patients with osteonecrosis

Patient	Sex	Age yrs	Diagnosis	Total skin dose R max	Treatment period in days	Skin dose/treatment in R	Cumulative skin dose R according to STRANDQVIST	Maximal absorbed bone dose in rad	Interval (yrs) between treatment and diagnosis of osteoradionecrosis
A	♂	18	Medulloblastoma	3 300	21	500	1 300	8 000	1
B	♀	18	Medulloblastoma	3 300	70	400	~ 1 000	8 000	9
C	♂	13	Medulloblastoma	4 200	63	300	1 000	10 000	1
D	♂	12	Medulloblastoma	3 200	105	400	~ 900	7 500	2
F	♀	9	*Medulloblastoma*	*4 500*	*35*	*300*	*1 500*	*11 000*	1
I	♀	7	Medulloblastoma	3 000	28	300	1 100	7 000	< 2
G	♂	3	Medulloblastoma	4 200	28	400	1 600	10 000	1
H	♂	53	Astrocytoma	4 000	84	500	1 [illegible]50	9 500	7
I	♂	50	Astrocytoma	3 300	28	400	1 100	5 500	< 2
K	♀	33	Astrocytoma	4 000	63	[illegible]00	1 100	9 500	6
L	♀	20	Astrocytoma	3 200	42	400	1 100	5 500	< 1
M	♀	19	Astrocytoma	4 000	63	600	1 250	9 500	4
N	♂	10	Astrocytoma	3 000	42	400	1 050	7 000	1
O	♂	24	Glioblastoma multiforme	*3 600*	*28*	*500*	*1 400*	*8 500*	*2*
P	♀	63	Oligodendroglioma ( )	3 400	28	400	1 250	8 000	< 2
Q	♂	14	*Malignant oligodendroglioma*	4 000	*70*	*500*	*1 250*	*9 500*	< 5

of osteonecrosis as well as the course of the lesions are indicated in Fig 1 Six of the patients (L P N O C and B) are still living 7 7 8 9 11 and 17 years after treatment

Sarcoma of the calvarium after irradiation In neither of the two cases of sarcoma to be described had any signs of other disease of the calvarium been observed before radiotherapy

Case 1 A girl aged 7 years with cerebral symptoms had roentgen evidence of a central calcified tumor In March 1956 the *patient* was operated upon with subtotal extirpation of a partly intraventricular tumor Histologic examination revealed a *teratoma* with development of *bone* cartilage and chorioid plexus-like structures Numerous mitoses and cellular atypia suggesting malignancy were noted

Postoperative roentgen treatment was given to three 6 cm × 7 cm fields (Fig 2 a) 170 kV

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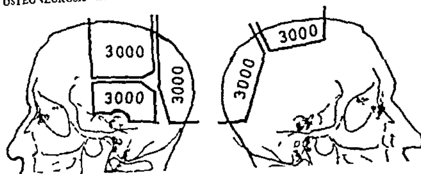
radiation in animals. The first such cases in human beings were described independently by BECK and by MARSCH in 1922, who reported 3 cases and 2 cases, respectively, of sarcoma of long bones, 3 to 8 years after their irradiation for tuberculosis. The number of published cases of osteosarcoma following irradiation has since increased to more than 100, large series have been published by HATCHER (1945), CAHAN et coll. (1948), SABANAS et coll. (1956), CRUZ et coll. (1957) and GOLDBERG et coll. (1963). Only 5 cases of sarcoma of the calvarium, however, are on record (SKOLNIK et coll. 1956, RAVENTOS et coll. 1960, MEREDITH et coll. 1960, and WENDE 1962). JÆNTZER (1937) induced an osteosarcoma of the cranium in rabbits by the application of radium, and BERG & LINDGREN (1961) described sarcoma of the cranium in the rabbit after roentgen irradiation.

Present material

Osteonecrosis of the calvarium. Roentgenograms of patients who had received a full course of radiation treatment during the period 1946—1958 for primary intracranial tumors were re-examined, and the changes observed were correlated with other findings. Roentgen examination after the conclusion of treatment had suggested osteonecrosis in 25 patients. In four of them, however, the further course indicated that the lesions were of infectious origin (suppuration and migration of sutures within 3 months of completion of treatment), in two the lesions proved to be metastases from medulloblastoma (changes also in other parts of the skeleton within 11 months of the conclusion of treatment), and in one patient re-examination of films taken before therapy disclosed that the changes, though then slight, had already commenced. The roentgenograms in one patient revealed necrosis developing into sarcoma and in another an osteolytic sarcoma without previous necrosis.

The material thus consisted of 16 patients with uncomplicated osteonecrosis and 2 patients (see below) with sarcoma.

Treatment was administered with 170 kV roentgen irradiation. The other radiologic data, sex distribution, age distribution and the diagnoses for which the 16 patients were treated are given in Table 1. A Thoraeus filter (HVL = = 1.5 mm Cu) was used in two patients and a filter of 0.5 mm Cu + 1 mm Al (HVL = 0.9 mm Cu) in the remaining patients. The skin doses ranged between 1 100 R and 4 500 R, the larger doses usually being delivered in several series of 2 to 4 weeks' duration at intervals of 4 to 6 weeks; one treatment was given daily (except Sundays) with the irradiation of one field per treatment. The intervals between the end of radiation treatment and detection



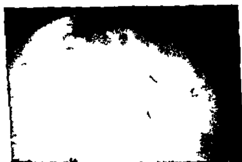
a



b



c



d



e

I g 2 Ca e 1 Osteone rosis and sarcoma a) Po tals and sk n do es in R b) Thinn ng of bone on l ft d n th t eated area 6 years after conclu on of treatment c) Lateral projection Patchy r egular d c lcificat on in th same ar a d) Seven months later Sl ght increase of the patchy d cal f at on e) Ten m onths later than (b) and one month before operation P ogression of the path logic hanges no periosteal react on

Fig. 1. Course of osteonecrosis in 16 patients.

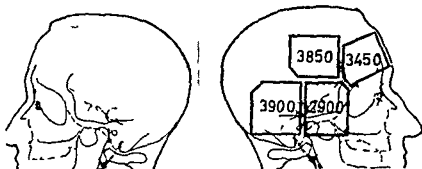
filter 0.5 mm Cu + 1 mm Al and FSD 60 cm for 35 days with a skin dose of 3 000 R, the calculated tumor dose being 3 900 to 4 500 R. The hair began to fall out after the patient had received 1 100 R/11 days and following treatment the irradiated areas were hairless. The patient afterwards felt well and did well at school.

In the spring of 1962, six years after the conclusion of treatment, a subcutaneous tumor began to grow rapidly in the temporal region down over the bone flap. The patient had headache but no other symptoms. Roentgen examination (Fig. 2 b and c) disclosed thinning of the bone in the area treated as well as patchy irregular areas of rarefaction suggesting osteonecrosis. *Biopsy* revealed a sarcoma.

The soft tissue tumor progressed and roentgen examination 7 months and 10 months later produced evidence of progress of the pathologic changes (Fig. 2 d and e). In February 1963 the patient was operated upon with subtotal extirpation of the sarcoma, which was growing into the middle and posterior thirds of the sinus and infiltrating the dura.

Histologic examination revealed pleomorphous sarcoma with formation of collagen fibrils but without definite osteoid tissue (Fig. 3). The patient died 9 months later and no autopsy was performed.

Case 2. A woman who had at the age of 25 developed neurologic signs. Five years later a cerebral tumor was evident in the right temporal region. In November 1958 the patient was



a



b



c

Fig. 4. Case 2. O t onecr s and sarcoma [illegible] rtal nd [illegible] nd es in R b) Postoperat e appe r n es [illegible] for o ntgen tr atment Opera ton d f t ta t lun powder in rted c) Two a nd 9 months aft r end of roentgen t [illegible] changes in the flap and r igh bo r ig bon of th r a tre ted d) Fur th r ar an 18 onth later Pr gress on of [illegible] nges



d

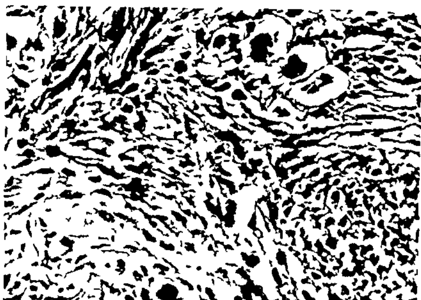


Fig. 3. Case 1. Polymorphocellular sarcoma with scanty fibrous fibers. No definite osteoid tissue. van Gieson. × 250.

subjected to operation with right sided resection of the temporal lobe and partial extirpation of a mandarin sized tumor. Histologic examination revealed an astrocytoma of intermediary type.

Three months after the operation, by which time the wound had healed well, roentgen treatment was started with 170 kV, filter 0.5 mm Cu + 1 mm Al and FSD 60 cm. Four fields 5 × 5 to 5 × 6 cm were irradiated (Fig. 4 a). The skin dose was 2 900 R to 3 850 R and the calculated tumor dose 5 200 R/40 days. The patient afterwards felt well and EEG indicated continuous regression.

Roentgen examination of the skull in 1959, 1960 and 1961 disclosed *no change in the position of the operation cavity* as judged by tantalum powder that was introduced. The last roentgen examination of the skull in 1961 revealed osteolytic changes *suggesting osteonecrosis* (Figs. 4c and 5a).

In March 1964, 5 years after the end of roentgen treatment, a tumor began *to grow rapidly* in the right temporal field where the skin dose had been 3 850 R/39 days. The *patient had no* symptoms to suggest recurrence of the cerebral tumor. Roentgen examination in July 1964 (Figs. 4d and 5b) disclosed progression of the lytic changes in the bone and a soft tissue tumor poor in blood vessels outside the suppressed bone flap. The lamina externa in the area appeared to be irregular.

The tumor was considered to be inoperable and the patient was treated with ^{137}Cs in a dose at 0.12 cm under the skin of 3 000 rad/14 days. The mass then regressed considerably. After the patient had received 1 800 rad, biopsy revealed that the growth was of cartilaginous consistency, shining white and poor in blood vessels. A metastatic lymph node near the right mandibular angle was present.

Histologic examination showed a fibrosarcoma (Fig. 6). When last seen, 4 months after the end of treatment, the patient had pulmonary metastases.

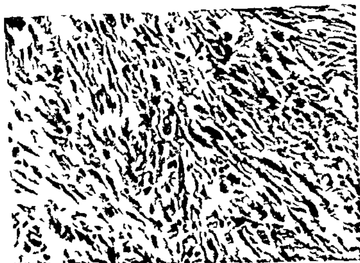


Fig 6 Case 2 Relatively well differentiated fibrosarcoma with delicate fibrils in the intercellular substance Haematoxylin and eosin × 250

The frequency of osteonecrosis varies from series to series CAMP & MORETON (1945) found 5 instances in 2 046 patients who had received roentgen radiation therapy for intracranial tumors but they stress that only a few were followed up roentgenographically KNITTEL (1935) reported necrotic changes in 9 out of 28 patients The poor prognosis of such tumors makes it difficult to assess the true incidence of necrosis

The present series of osteonecrosis included 7 patients with medulloblastoma and 6 with astrocytoma During the same period 35 patients with medulloblastoma and 55 with astrocytoma (Fig 7) had received roentgen treatment Osteonecrosis was thus demonstrated in 20 % of the patients with medulloblastoma and in 11 % of those with astrocytoma Since the 3 year survival rate of the two groups was 20 % and 75 % respectively the frequencies observed for osteonecrosis must be minimal especially since some of the 35 patients with medulloblastoma were not examined roentgenographically after radiotherapy The discrepancy between the frequency of necrosis in the two groups may be explained by differences in age distribution (Fig 7) the radiosensitivity of the neurocranium being higher in early age

Onset and course Most records indicate that the patients were not regularly examined roentgenographically after the conclusion of radiation treatment The reports are therefore of only limited value in the assessment of the latency of osteonecrosis but changes have been described 1 to 20 years after treatment

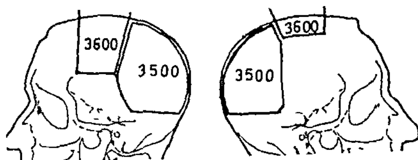


Fig. 5. Case 2. a) Frontal projection 2 years and 9 months after end of treatment. b) Frontal projection after further 2 years and 8 months. Displacement of flap medially compared with previous investigation; slight irregularity in tabula externa of flap.

Discussion

Frequency of osteonecrosis. Osteonecrosis (radiation osteitis) of the skull following irradiation has been described in both sexes (7 males, 18 females) and at all ages ranging from early infancy to 60 years. The present material consisted of 10 males and 6 females, aged 3 to 63 years.

Osteonecrosis is probably more common than hitherto supposed. It is well known from clinical experience as well as from experiments by BADE & KUNTSCHER (1939) that even marked histologic changes of the skeleton are not always roentgenologically demonstrable. The condition per se does not appear to produce any symptoms and probably often runs a subclinical course causing changes mainly in weight bearing bones. BORGSTRÖM & GYNNING (1957) reported vertebral compression to be common (12 out of 19) in patients who had survived rotational roentgen treatment for oesophageal cancer for more than 3 years. The commonest site of fracture in necrotic bone is the femoral neck, where the predisposition to fractures is well known. In an epidemiologic investigation, ALFFRAM (1964) gave osteonecrosis as a causal factor of fractures of the femoral neck in only 15 of 1 664 cases.



a



b



c

Fig 8 Osteonecrosis in patient O (see Table 1) a) Portals and skin doses in R b) Immediately after end of roentgen treatment Operation defects tantalum powder inserted c) Three years and 8 months later Widespread patchy decalcifications in the areas treated

The course was followed from 7 months to 5 years following the end of treatment in six patients (D F I L O and P) in whom necrosis progressed Fig 8 represents the development of osteonecrosis in patient O Supervening necrosis was also noted in patients D and O but in patient B the necrosis was stationary from 9 to 15 years after treatment The changes became static as early as one year after treatment in four patients (C E G and N) and in two of them (C and N) in whom the course was followed for several years the changes even regressed in that they became smaller more calcified and less distinctly outlined Figs 9 and 10 depict the course in patient C Although regression of osteonecrosis of the cranium has not previously been described it is recognized that fractures of radionecrotic bone may heal (BIRKNER 1953)

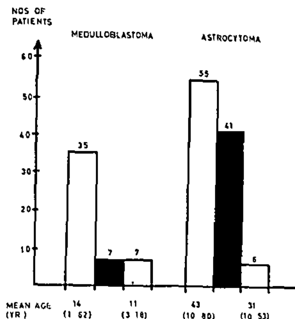


Fig 7 Number of patients given roentgen treatment between 1946—1958 with 3 year survival Frequency of uncomplicated osteo necrosis and age distribution are given

TOTAL NUMBER OF PATIENTS TREATED
STILL LIVING AFTER 3 YEARS
NUMBER OF PATIENTS WITH KNOWN NEUROCRANIAL OSTEORADIONECROSIS

SALVINI (1956) and WACHTLER (1961) observed that the changes progressed for 1 to 4 years after the end of treatment, and re examination after a further interval of 1 to 3 years revealed no further progression According to KOLÁR & VRABEC (1957), additional irradiation stimulates progression of the necrotic changes None of the patients of the present series received further irradiation of the cranium

Since 1950, roentgenograms have been obtained regularly after treatment in the present series The course was followed roentgenographically for several years in eight of the 16 patients but for only a short period or only on one occasion in the remaining eight (Fig 1) Roentgen examination at 8, 12 and 9 months, respectively, after the conclusion of treatment in patients F, I, and P, respectively, disclosed no signs of osteonecrosis Such changes were however, evident on examination 18 21 and 22 months after treatment In the remaining 13 patients, osteonecrosis was demonstrated roentgenographically at the first follow up examination after the conclusion of treatment The first roentgen examination after treatment in six (A C E G, L and N) of these 13 patients was performed one year after the end of treatment Bone necrosis was thus discovered within one year after treatment in 6 patients after 18 months to 3 years in 5, and after more than 3 years in the remaining 5 patients

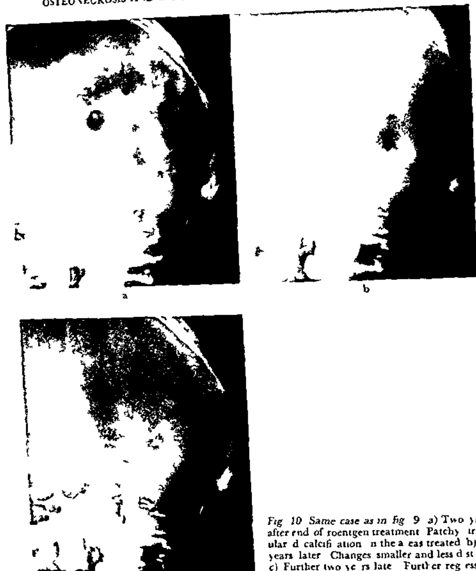


Fig 10 Same case as in fig 9 a) Two years after end of roentgen treatment Patchy irregular decalcification in the areas treated b) Six years later Changes smaller and less distinct c) Further two years later Further regression

KNITTEL (1955) KOLAR & VRABEC (1957) and HAUBRICH & BREUER (1958) The osteoblasts and osteoclasts are markedly reduced in number and sometimes altogether absent The trabeculae in the spongiosa and the haematopoietic parenchyma are replaced more or less by granulation tissue which may be richly vascularised spongy or more fibrous The compact bone may be thickened Stasis thrombosis and fibrosis of the blood vessels are sometimes present

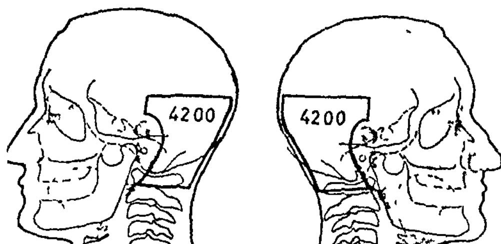


Fig. 9. Osteonecrosis in patient C (see Table 1). Portals and skin doses in R.

It is difficult to say anything definite about the relationship, if any, between the development of necrosis and the dose given, owing to the variation in the number of fields used and the duration of treatment. Radium or roentgen treatment has been given in previously published cases. The largest doses used were about 21 500 R in the course of 4 to 5 years (MIRIMOVA & ANDREEVA 1962, and BROTSLAVSKIJ 1962) delivered with 160 to 180 kV roentgen. Superficial and deep therapy were used, with over 20 000 R/10 years as skin dose, in HAUBRICH & BREUER's (1958) patients. One of KOLAR & VRABEC's patients received superficial therapy by the Chaoul method with 8 900 R. In other cases on record the dose ranged from 1 100 to 7 100 R. An attempt was made to form an opinion between the dose given and the development of osteonecrosis (see Table 1). Total skin doses between 3 000 and 4 500, and cumulative doses between 900 R and 1 600 R, given for 21 to 42 days, appeared to favour the development of necrosis although it sometimes occurred even when treatment was administered in two series for 63 to 105 days with skin doses between 3 200 and 4 000 R. The necrosis sometimes progressed and at other times regressed. No correlation was evident between the size of the dose and the course of the destruction in the present material. It is probable that the occurrence or non-occurrence of necrosis depends more on individual factors than on the actual size of the dose given, provided that overdosage can be excluded. Age at the time of treatment appears to be an important factor, and both of the two patients in whom the necrosis regressed were young (13 and 10 years) but only one had received a relatively small dose.

Pathogenesis. Histologic examinations of osteonecrotic lesions have been published by BALLI & BARBANTI SILVA (1931), CAMI & MORETON (1945),

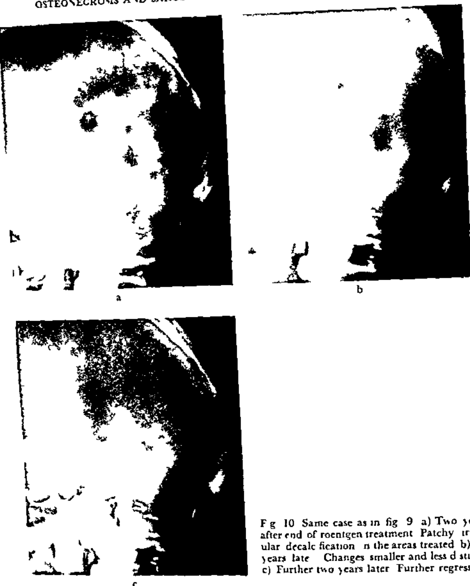


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Various explanations of the causal mechanism of osteonecrosis have been offered. According to EWING (1926), the arrangement of the blood vessels in bones in the narrow Haversian channels render the bones very sensitive to radiation. He observed that irradiation of bones produced vascular injury with the formation of sclerotic connective tissue in the marrow cavity and disappearance of the osteoblasts. ZOLLNER (1941) stated that the osteoblasts and osteoclasts in irradiated bone disappeared and concluded that the normal equilibrium between bone resorption and new formation of bone is thereby disturbed. When the dose delivered is small, it is mainly the osteoclasts that are injured and then regeneration still appears possible. But our patient C, in whom the osteonecrosis regressed, had received as large a skin dose as 4 200 R; only one of the other patients had been given a larger dose. WIELAND (1956) and DAHL (1934, 1935) reported, like ZOLLNER (1941), that osteocytes are radiosensitive. BADE & KUNTSCHER (1939) irradiated the femoral neck in dogs and noted that even small doses (2 400 R/60 days), producing only partial epilation, had a severe effect on the skeleton with complete suppression of the capacity of injured bone to recover. DAHL (1934, 1935) made the same observation in young rats, and observed that growing osseous tissue is more radiosensitive than most other tissues.

Radiation treatment was followed by epilation in all the patients of the present series, by atrophy of the skin and pigmentation in seven (A, F, G, H, I, K and Q), and by marked teleangiectasis in four patients (G, H, K and Q). Three patients, aged between 9 and 13 years (C, I and N), in whom necrosis had been detected one year after treatment, had no skin atrophy, pigmentation or teleangiectasis. These patients, like the animals in the experiments, were young, i. e. in a period of life when bony tissue may be more radiosensitive than the skin, as known from the inhibition of growth observed on irradiation of the epiphyses of long bones. In the light of these observations it is remarkable that none of the irradiated children presented evidence of any inhibition of growth of the cranium in the irradiated area. The balance between the resorption and new formation of bone thus appeared to have been relatively normal. This may be explained by the fact that these bones are membranous and not cartilaginous.

Surgical trauma. The site of the necrosis has often been the femoral neck, resulting in a fracture, in the cases of osteonecrosis reported. This may be explained by the already impaired circulation of this part of the skeleton in advanced age owing to obliteration of the acetabular artery. In analogy changes in the calvarium might be expected to be situated in or near the bone flap. The changes proved most marked in the bone flap in three (O, R and N)

Table 2

Seven patients with irradiation sarcoma of the cranium

	Sex	Age at time of treatment in years	Dose	Interval in years between end of treatment and diagnosis of sarcoma	Site	Histologic type of sarcoma
Skolnik et coll 1956	♂	16	Roentgen skin dose 6 000 R/41 days	3 1/?	Temporal	Osteosarcoma
	♀	1	Radium 9 600 mghrs 9 months	10	Frontal	Chondrosarcoma
Meredith et coll 1960	♀	51	Roentgen skin dose 1 200 R/8 days	6	Temporal	Osteosarcoma
Ra e tos et coll 1960	♀	27	Roentgen skin dose 2 100 R/45 days Maximal absorbed bone dose = 9 300 rad	17	Frontal	Fibrosarcoma
Wen e 1962	♀	23	Roentgen skin dose 4 400 (?) R/4 years	17	Frontal	Fibrosarcoma
Present material Case 1	♀	7	Roentgen skin dose 3 000 R/35 days Maximal absorbed bone dose — 7 100 rad	6	Parietal	Fibrosarcoma
Present material Case 2	♀	25	Roentgen skin dose 2 900 to 3 850 R/40 days Maximal absorbed bone dose = 12 000 rad (hot spot)	5	Temporal	Fibrosarcoma

of the patients but considerable changes were also evident outside the flap (Fig 8) In three of the patients (D G and P) only diagnostic cerebral biopsy was done via a burr hole in two (E and F) only a small craniotomy was performed and one patient (M) was not subjected to operation (the histologic diagnosis in this case was obtained at autopsy) but clear cut osteonecrosis was evident in bone not damaged by surgery In several of the patients (Figs 9 and 10) the changes were situated far from the operation field No definite relationship was thus evident between osteonecrosis and surgical trauma

Sarcoma of the skull following irradiation The five cases of sarcoma traced in the literature and the two described in this communication are summarized in

Table 2. These patients, one male and six females, were 1 to 51 years old at the time of treatment and 6 of them were under 30. Like the patients with uncomplicated necrosis, they were thus mainly young at the time of treatment. The predominance of females may be due to chance. The interval between the end of treatment and the clinical onset of the sarcoma varied between 3 1/2 years and 17 years, a range agreeing well with that observed for sarcoma due to irradiation in other parts of the skeleton, i. e. 1—24 years.

The skin doses, given to patients in whom osteosarcoma has later developed, range between 1 500 and 11 500 R (usually between 4 000 and 6 000 R). The patients with sarcoma of the calvarium had received skin doses ranging between 1 200 and 6 050 R. The calculated absorbed bone dose in the case of RAVENTOS et coll. (1960) was 9 300 rad and in the present cases 7 100 and 12 000 rad. The interval between treatment and the development of sarcoma does not appear to vary with the skin dose given.

The tumors often originated from previously diseased bone, usually tuberculous bone or bone affected by giant cell tumors in cases published of irradiation of sarcoma in bony tissue other than the cranium. It is noteworthy that in the present two cases the tumors were situated mainly in the bone flap, which in Case 1 appeared to have healed well, while in Case 2 considerable resorption had occurred along the line of the craniotomy. A sarcoma however had not developed in the region of any surgical defect in the cranium in any of the cases previously published.

According to JAFFE (1958), and ACKERMAN & SEJUT (1962), an irradiation sarcoma of bone is usually a fibrosarcoma, but sometimes the growths appear to be osteosarcomas or chondrosarcomas. The tumors in the 7 patients under discussion were fibrosarcoma in 4, osteosarcoma in 2 (including one with spicule formation (SKOLNIK et coll. 1956)) and chondrosarcoma in one patient. The question then arises as to whether the fibrosarcomas had developed from the bone or from irradiated soft tissue such as the galea or dura. A number of factors suggest that the growths had commenced in irradiated bone. First and foremost, the dose absorbed is largest in osseous tissue. Further, a clear relationship between the development of sarcoma and radiation necrosis was evident in several patients. In RAVENTOS' (1960) case, roentgenography disclosed this radiation reaction 7 years before the appearance of the sarcoma, and in WENDE's (1962) case necrosis was verified histologically.

Case 2 of the present series had marked necrosis for nearly three years before the occurrence of the sarcoma and similar changes, though slight, were evident in association with the development of the sarcoma in Case 1. All the tumors grew extensively in the osseous tissue. In Case 1, in which this was demonstrated at operation, it was even more extensive than suggested by the roentgenograms

(in which evidence of a sarcoma was actually not strong) This widespread growth in the bone suggests that these fibrosarcomas are of osseous origin The data on osteonecrosis are less reliable in the cases of osteosarcoma and chondrosarcoma neurocranii MEREDITH et coll (1960) considered it remarkable that a large osseous destruction beneath the tumor could not be demonstrated roentgenologically (roentgenograms not published) In the two patients of SKOLNIK et coll the tumors were situated temporally and frontally near the base of the skull which made it difficult to demonstrate necrosis if present radiographically

CRUZ et coll (1957) reported advanced osteonecrotic lesions in only two of 11 cases of irradiation sarcoma of bone outside the neurocranium, and they concluded that sarcoma may develop in bone moderately injured while severely injured bone has not the capacity to react with neoplastic transformation It is not known in our cases whether the radiation lesion from the pathologic point of view were true necrosis or radiation osteitis with atrophy of bone

Complicated versus uncomplicated osteonecrosis The diagnosis of osteonecrosis was made roentgenologically in the present cases as in others on record The changes are multiple irregular lytic and confined to the irradiated areas The postoperative decalcification sometimes seen after craniotomy alone is of a clearly different appearance The conditions to be considered in the differential diagnosis are infectious complication with osseous necrosis, growth of cerebral tumor per continuitatem, metastases or myeloma and irradiation sarcoma Apart from metastases from a medulloblastoma there is no reason to consider the possibility of bone metastases from malignant cerebral tumors When infectious complications occur, they usually do so within a few months One of our patients with radionecrosis however, developed an abscess in the operation scar (he had bilateral osteonecrosis) 4 years after treatment, but none of the other patients had any signs of skin ulceration or osteitis

Neurologic symptoms and signs which occurred in most patients with osteonecrosis could be ascribed to the basic disease or to changes in the brain due to the therapy (LINDGREN 1958) The soft tissue swelling was the initial symptom in the present two cases of radiosarcoma It was also found that uncomplicated osteonecrosis progressed slowly during the first years and then became stationary or even regressed Progression of roentgenologic changes more than five years after irradiation should thus suggest sarcoma The roentgenologic changes may however be very subtle

Osteonecrosis alone is evidently of no clinical importance but when complicated by sarcoma the prognosis is not bright with rapid growth and often with

pulmonary metastases The present two cases followed the same hopeless course as other cases of sarcoma of the cranium The risk of sarcoma is small but it is one of the many factors that should be considered before deciding upon radiation treatment of intracranial tumors especially in young subjects

SUMMARY

Radionecrosis of the skull in a material of 16 patients is described The condition was more common after irradiation of children and young people and the changes were not related to surgical trauma or the radiation dose delivered A consideration of two patients with sarcoma of the skull indicated that soft tissue swelling or progression of cranial necrosis five years after irradiation or later should suggest a malignant change

ZUSAMMENFASSUNG

Sechzehn Falle von Radionekrose des Schadels werden beschrieben Das Krankheitsbild war haufiger in Kindern und jungen Leuten es hatte keinerlei Beziehungen zu Trauma oder zur Strahlendose Zwei Falle von Sarkom zeigten dass Weichteilschwellung oder eine fortschreitende Nekrose funf Jahre nach Bestrahlung Zeichen einer malignen Veranderung sind

RÉSUMÉ

Description de la radionecrose du crane sur 16 cas Cette affection est plus fréquente apres l irradiation d enfants et de jeunes et les lésions sont sans rapport avec le traumatisme chirurgical ou la dose d irradiation L étude de deux malades atteints de sarcome cranien montre que l epaississement des parties molles ou la progression de la nécrose cranienne cinq ans ou plus apres l irradiation doit faire penser a une transformation maligne

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EFFECT OF CORTISONE ON ^{131}I-THYROXINE IN LIVER AND BILE

by

B Blomstedt and J Einhorn

An earlier study on human subjects disclosed that large doses of cortisone increased the peripheral degradation of thyroxine while the slope of the disappearance curve for thyroxine in the blood decreased (Blomstedt & Einhorn 1965) A possible reason for this effect is that the cortisone mobilized thyroxine from extravascular depots to the blood stream Since the liver and the enterohepatic circulation are the largest extravascular depots for injected thyroxine (Gross & Leblond 1950 Myant & Pochin 1950 Albert & Keating 1952 Friis 1958) it would seem likely that part of the thyroxine mobilized to the blood during the administration of cortisone is absorbed from this pool

A large part of the radiothyroxine injected in the rat is taken up in the liver and excreted with bile into the intestine most of the thyroxine excreted is conjugated to glucuronic acid in both the rat (Roche et coll 1954 Taurog 1954) and man (Myant 1956)

These experiments have been conducted to study the effect of cortisone on

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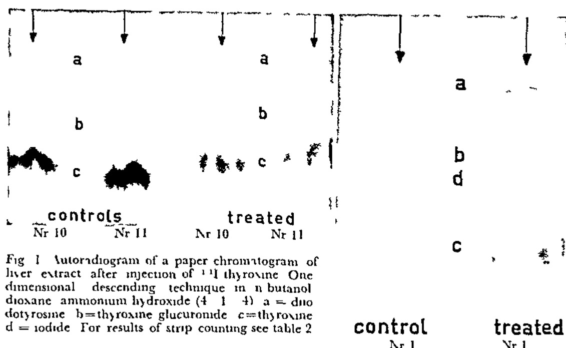


Fig. 1. Autoradiogram of a paper chromatogram of liver extract after injection of ^{131}I thyroxine. One dimensional descending technique in n butanol dioxane ammonium hydroxide (4 : 1 : 4). a = diiodotyrosine, b = thyroxine glucuronide, c = thyroxine, d = iodide. For results of strip counting see table 2.

the total amount of thyroxine in the liver, on the excretion of thyroxine with the bile and on the relationship between the total thyroxine and the amount conjugated to the glucuronic acid in the liver and bile.

Material. The experiments were conducted in 48 male white rats of Sprague Dawley strain, each weighing about 300 g. The liver study was performed in 40 of these, and the bile study in 8. All rats were maintained on constant feeding and temperature.

Methods. The ^{131}I thyroxine was supplied by Abbott Laboratories, Oak Ridge, U.S.A. The specific activity was 24 to 48 mCi/mg. The solutions were stored at 4° C and used within one week of receipt. They were checked by chromatography before use and only solutions in which at least 94 per cent of the radioactivity was derived from ^{131}I thyroxine were used. A dose of radioactivity of 6 μCi/100 g rat weight was given as a single intramuscular injection to each rat.

Cortisone acetate (Upjohn) was administered by intramuscular injection. The effect of cortisone on the total amount of thyroxine in the liver was studied in 20 rats which received ^{131}I thyroxine. Ten of them received 10 mg cortisone daily during seven days, starting from the day the tracer was injected. The remaining ten rats constituted a control group. Nine days after the ^{131}I thyroxine administration the animals were sacrificed by anaesthetizing with ether followed by bleeding. The liver was removed immediately and its total

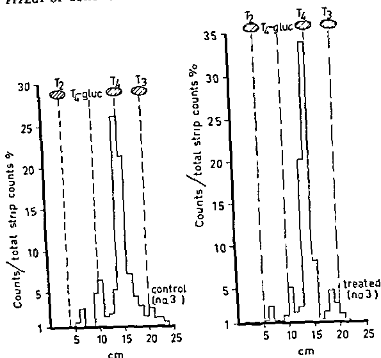


Fig 2 Chromatogr phy of l ver extract after njection of I thyrox ne One d mensional desce iding technique n n butanol dioxane ammonium hydrox d (4 1 4) Chromatograms strip counted cpm/cm expressed as a percent age of total radioactivity of the strip T = diiodotyrosine T = triiodothy on ne T = thyroxine T gluc thyroxine glucuronic ac d

radioactivity determined in a well type scintillation counter (Tracerlab) with 350 000 counts per minute and microcurie above a background of 20 cpm

The effect of cortisone on the relationship between total thyroxine and the amount coupled to glucuronic acid in the liver was studied in another 20 rats after the administration of ^{131}I thyroxine Ten rats received 5 mg of cortisone every 12 hours the remaining 10 rats constituting a control group two of these rats were given physiologic saline at the same time as the others received the cortisone The rats were examined in pairs — one cortisone treated animal and one control After 72 hours the animals were sacrificed as in the first investigation the liver being removed immediately and its total radioactivity determined The organ was homogenized in a water bath at 0 C after addition of sodium deoxycholate (SYLVEN & MALMGREN 1957) stable thyroxine was added as a carrier to the homogenate and after acidifying to pH 2 5 it was extracted repeatedly with *n* butanol At the first extraction the butanol was saturated with sodium thiosulphate to inhibit oxidation of

Table I

Rf values of iodated amino acids based on strip counting after one dimensional paper chromatography of liver extract with n butanol dioxane 2N ammonium hydroxide (4 : 1 : 4). T_2 = diiodotyrosine, T_4 gluc = thyroxine glucuronic acid, T_4 = thyroxine

Rat pair No	Controls			Cortisone treated		
	T_2	T_4 gluc	T_4	T_2	T_4 gluc	T_4
1	0.18	0.32	0.51	0.20	0.32	0.54
2	0.19	0.33	0.48	0.21	0.33	0.45
3	0.21	0.32	0.46	0.21	0.33	0.44
4	0.21	0.32	0.42	0.19	0.32	0.33
5	0.22	0.35	0.46	0.20	0.36	0.52
6	0.17	0.29	0.45	0.17	0.30	0.50
7	0.18	0.32	0.41	0.18	0.33	0.42
8	0.18	0.29	0.41	0.18	0.31	0.41
9	0.17	0.30	0.41	0.17	0.31	0.40
10	0.19	0.33	0.45	0.16	0.31	0.39
Mean	0.19	0.32	0.45	0.19	0.32	0.45

the iodine. The mean yield of radioactivity from the liver extraction was 71.6 per cent for the controls and 72.4 per cent for the rats receiving cortisone. The supernatant was evaporated to dryness, the dry residue was taken up in a mixture of *absolute alcohol and strong ammonium hydroxide* (3 : 1) and placed on Whatman paper No. 1. The paper chromatographic separation was performed by the one dimensional technique with a mixture of *n* butanol, dioxane and 2N ammonium hydroxide (4 : 1 : 4) as solvent. The position of the radioactivity on the chromatogram was determined by strip counting or autoradiography. The activity peaks were identified by running parallel with the sample, non radioactive standards, consisting of diiodotyrosine, 3,5,3 triiodothyronine, thyroxine and of radioiodine. Well defined activity peaks were obtained corresponding to diiodotyrosine, thyroxine glucuronide and free thyroxine (Figs 1 and 2), in some cases iodide and triiodothyronine were also detected. The radiothyroxine glucuronide was identified by its Rf value. The separation of the radioactive substances by paper chromatography was good and the Rf values for the compounds were practically constant (Table 1). The Rf values for free thyroxine and that bound to glucuronic acid in the liver extracts were in close agreement with values reported in earlier studies on rat bile (ROCHE et coll. 1951, BLOMSTEDT & NEUJAHR 1961).

In the study on the bile, an external fistula was placed in the common

Table 2

Paper chromatography of liver extract the percentage of the radioactive compounds based on strip counting T_4 gluc = thyroxine glucuronic acid and T_4 = non-conjugated thyroxine The values in the last column in each group denotes the percentage of radiothyroxine in the liver conjugated to glucuronic acid

Rat pair No	Controls: T gluc per cent	Controls: T per cent	Controls: $\frac{T_4 \text{ gluc} \times 100}{T_4 \text{ gluc} + T}$	Cortisone treated: T gluc per cent	Cortisone treated: T per cent	Cortisone treated: $\frac{T \text{ gluc} \times 100}{T \text{ gluc} + T}$
1	17 3	47 5	27	5 4	74 1	7
2	17 5	38 3	31	6 8	57 8	10
3	11 4	67 6	14	6 7	62 0	10
4	10 2	65 0	14	8 1	54 4	13
5	14 0	47 5	23	8 4	53 7	14
6	11 0	66 3	14	4 8	56 1	9
7	5 4	53 8	9	2 5	64 8	4
8	4 6	68 6	6	2 2	68 3	3
9	6 9	42 8	14	3 6	56 3	6
10	7 6	49 5	13	5 8	54 6	10
Mean	10 6	54 7	16 5	5 4	60 4	8 6

bile duct and was drained completely When the bile had begun to flow again ¹³¹I thyroxine was injected usually 2 to 3 hours after operation Four animals were given 5 mg of cortisone every 12 hours for 48 hours beginning at the time the thyroxine was injected Four rats serving as controls received ¹³¹I thyroxine but no cortisone the bile was collected at 8 hour intervals and the total radioactivity determined The bile specimens obtained from two controls and two cortisone injected rats after 8, 16 32 and 48 hours were subjected to chromatographic examination as was the pooled bile of each rat Chromatography was performed without previous extraction and the methods were the same as for the liver analysis

Results

The mean total radioactivity in the liver of ten control rats sacrificed 9 days after the administration of ¹³¹I thyroxine was 3 322 ± 165 4 cpm and in ten cortisone treated rats 2 466 ± 157 2 cpm The difference was statistically significant ($p < 0\ 01$) The difference was also significant when the radio activity per gram liver tissue was calculated (298 ± 25 9 cpm and 190 ± 10 5 cpm $p < 0\ 01$) and when the radioactivity in the liver was calculated in relation to the ¹³¹I dose administered ($p < 0\ 01$)

About 16 5 per cent of the radiothyroxine in the liver was bound to the

Table 3

Paper chromatography of pooled bile: the percentage of the radioactive compounds based on strip counting. T_4 gluc = thyroxine glucuronic acid. T_4 = non conjugated thyroxine. The values in the last column in each group denotes the percentage of thyroxine in the bile that is conjugated to glucuronic acid

Rat pair No	Controls			Cortisone treated		
	T_4 gluc per cent	T_4 per cent	$\frac{T_4 \text{ gluc} \times 100}{T_4 \text{gluc} + T_4}$	T_4 gluc per cent	T_4 per cent	$\frac{T_4 \text{ gluc} \times 100}{T_4 \text{ gluc} + T_4}$
11	49.6	3.9	92.7	63.5	3.4	94.9
13	62.4	2.1	96.7	43.3	4.6	90.4
15	56.2	2.1	96.4	58.4	1.2	98.0
17	56.3	1.4	97.6	53.1	1.3	97.6
Mean	56.1	2.4	95.8	54.6	2.6	95.0

Table 4

Paper chromatography of bile samples drawn at different times after the administration of ¹³¹I thyroxine: the percentage of the radioactive compounds based on strip counting. T_4 gluc = thyroxine glucuronic acid. T_4 = non conjugated thyroxine. The values in the last column denotes the percentage of thyroxine in the bile conjugated to glucuronic acid

Rat pair No	Hours after injection of ¹³¹I thyroxin	Controls			Cortisone treated		
		T_4 gluc per cent	T_4 per cent	$\frac{T_4 \text{ gluc} \times 100}{T_4 \text{ gluc} + T_4}$	T_4 gluc per cent	T_4 per cent	$\frac{T_4 \text{ gluc} \times 100}{T_4 \text{ gluc} + T_4}$
15	8	50.7	4.8	91	46.4	1.5	97
	16	54.7	2.0	96	58.5	2.1	97
	32	58.0	0	100	60.5	0	100
	48	47.9	1.1	98	51.9	4.0	93
17	8	52.8	2.0	96	42.9	2.0	96
	16	63.1	1.5	98	55.4	2.4	96

glucuronic acid in the liver extracts from the control rats sacrificed 72 hours after administration of ¹³¹I thyroxine, the corresponding value for the rats receiving cortisone being 8.6 per cent. The difference was statistically significant ($p < 0.001$). Furthermore, the amount of thyroxine glucuronide in relation to the total radioactivity detected in the liver, was in all pairs less for the cortisone treated rat than for the control (Table 2). The difference between the groups was statistically significant ($p < 0.01$). The amount of thyroxine not coupled to glucuronic acid was more variable (Table 2). The results for

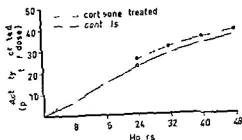


Fig 3 Cumulative excretion of radioactivity with the bile after administration of ¹³¹I thyroxine expressed as a percentage of the ¹³¹I dose administered
-- The mean of 4 cortisone treated rats
—— *The mean of 4 control rats*

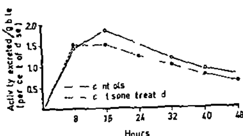


Fig 4 Radioactivity excreted per gram bile at 8-hour periods after administration of ¹³¹I thyroxine expressed as a percentage of the ¹³¹I dose administered
-- Mean of 4 cortisone treated rats
—— Mean of 4 control rats

the two control rats receiving physiologic saline (Nos 5 and 6) did not differ from those for the other controls

The cumulative excretion of radioactivity with the bile between the control and cortisone groups showed no significant difference (Fig 3) The radioactivity per gram bile from samples drawn at different times is given in Fig 4

The radiothyroxine in the bile was conjugated to glucuronic acid to a much greater extent than that in the liver About 95 per cent of the radiothyroxine in the bile in both the cortisone and control rats was conjugated to glucuronic acid (Tables 3 and 4)

Discussion

The fact that the effect of cortisone on the total amount of thyroxine in the liver was determined after 7 days of cortisone administration but the effect on the biliary excretion of thyroxine after only two days may have influenced the results The amount of thyroxine in the bile after 7 days of cortisone administration may be decreased The biliary fistula experiments could however not be continued more than two days because of the altered general condition of the rats The experiments also prevented the enterohepatic circulation of thyroxine which may have affected the results

The administration of large doses of cortisone to rats significantly decreased the total amount of ¹³¹I thyroxine in the liver Since no increase in the biliary excretion of radioactivity could be observed in the cortisone treated rats (Fig 3) there remain two possible explanations to the reduction of thyroxine in the liver (1) changed distribution of the hormone with increased transport of thyroxine from the liver to the blood, or (2) increased degradation of thyroxine in the liver The results do not permit of any definite conclusions,

but an increase in the transport of thyroxine from the liver to the blood is in agreement with previous studies in man, since it offers an explanation for the decreased slope of the disappearance curve for thyroxine in the blood observed simultaneously with its increased peripheral degradation in man during cortisone administration (BLOMSTEDT & EINHORN)

A relative decrease of thyroxine coupled to glucuronic acid in the liver in relation to its total amount following cortisone administration is also in agreement with this hypothesis The release of thyroxine from the glucuronic acid conjugate ought to play a part in a supposed process of reabsorption of thyroxine to the blood, since thyroxine glucuronide does not occur in the blood except in obstructive jaundice (ROCHE et coll 1954, VANNOTTI 1957)

The results indicate that large doses of cortisone accelerate the release of thyroxine from the glucuronic acid in the liver and influence the excretion of thyroxine to the blood

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This work was supported by the Swedish Medical Research Council and Karolinska Institutet The authors take this opportunity of thanking Mrs B Brodin for her technical assistance

SUMMARY

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Experimente an Ratten zeigen dass grosse Dosen von Cortison Thyroxin aus Glucuronsäure in der Leber freisetzen und die Menge von Thyroxin in der Leber reduzieren Die Cortison dosen hatten keinen Einfluss auf die Radio Aktivität der Gallenausscheidung

RÉSUMÉ

L expérimentation sur des rats montre que les fortes doses de cortisone séparent la thyroxine de l acide glycuronique dans le foie et reduisent la quantité de thyroxine dans le foie L administration de cortisone n a pas eu d effet sur la quantité de radio activité excrétée avec la bile

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FROM THE RADIOTHERAPY CLINIC (DIRECTOR PROF S MUSTAKALLIO) OF THE UNIVERSITY CENTRAL HOSPITAL OF HELSINKI, FINLAND

CROSS-SECTION DIAGRAMS IN PLANNING ROENTGEN TREATMENT

by

REIJO RINNE

A reliable cross section diagram is essential in planning roentgen treatment However, the shape of the recumbent human body may often depend on whether the subject is prone or supine and the location of the tumour may often also change In spite of this it is common usage to establish only one cross section, particularly if this is made with sufficient accuracy

Flexible metal wire by means of which the contours of the patient are transferred to paper, has been used to mark the width and thickness of the patient and thus to establish the section A more complicated drawing device outlining the contours of the patient s body directly on paper, the pointer of the appliance being moved along the body of the patient, has also been employed The former method is rather quick, even if somewhat inaccurate, the latter more precise although relatively slow We have for several months been using a device that ensures fairly quick and comparatively accurate cross section diagrams of the human form

The whole apparatus is made of aluminium The frame is provided with 47 aluminium prongs, with a length of 10 cm at 1 cm intervals The frame may

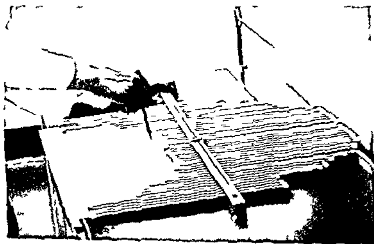
Submitted for publication 15 September 1965



F g 1 The de ice placed so that the coloured pl st c cap ind cating the centre coincides w th th centre axis of the pat ent A level at the middle of the f ame helps to keep the device horizontal the pegs are fixed by a lock



F g 2 The lock is released and the pegs lowered to fit the shape of the body The bars indicate the thickness of the patient (unless an air sp ce is left betw en the pat ent and base) the position is locked



F g 3 The de ice s removed to d awing paper and the hape is outl ned the procedur for draw g th dor al s de s the same Some d stort on may appear n the lat al parts of the drawings of the ventral and do sal aspects but this is u u ll of l ttle con equence The lo k buttons of the lock rails lie at both ends of the frame

be locked or the needles released by pressure of the thumb. A level affords visual evidence of its horizontal positioning.

It is important that the bedding on which the patient lies is hard, it is otherwise not possible to make the thickness measurement. Since the centre line of the sternum or the processus spinosus is not always on the geometric centre line of the patient's body, it is necessary to ensure that in using the device the number of measuring prongs falling down on both sides is equal, possible deformities of the patient's body will thus be more correctly registered. The thickness of the patient is best measured when the underside is firmly pressed against the bedding. With the patient lying supine, an air space is often present under the lumbar lordosis, and when prone, an air space may exist under the symphysis or the sternum.

After the prongs have been dropped over the patient and locked, the appliance is placed on the drawing paper and the contours are outlined. A mark that indicates the thickness of the patient is drawn at the sites where the prongs reach the bedding and from this mark the contour of the opposite side is then outlined. The tops of the prongs are provided with plastic caps, coloured at intervals of 5 cm, in order to facilitate the determination of the centre point and contours.

SETÄLÄ (1965) has published a most accurate and delicate apparatus for body contouring.

SUMMARY

A measuring device for obtaining cross section diagrams of patients undergoing radiotherapy is described.

ZUSAMMENFASSUNG

Ein Instrument zur Herstellung von Querschnittsdiagrammen für die Röntgentiefentherapie wird angegeben.

RÉSUMÉ

Description d'un dispositif permettant de tracer des coupes transversales de malades soumis à la radiothérapie.

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SETÄLÄ K.: Automatic body contouring unit for dose planning in radiotherapy. Acta radiol. Ther. Phys. Biol. 3 (1965), 361.

FROM THE DEPARTMENT OF RADIOPHYSICS (DIRECTOR: C. B. MADSEN) AT THE RADIUM CENTRE (DIRECTOR: PROF. S. KAAE), THE MUNICIPAL HOSPITAL OF AARHUS, DENMARK

COMPUTER PROGRAM FOR DOSE PLANNING WITH ANALYTICAL REPRESENTATION OF RADIATION FIELDS

by

OLE KALNAES

The digital computer has recently become most useful at many centres for radiation treatment planning. STERLING, PERRY & KATZ (1964) worked out a system including the use of analytical expressions for the radiation fields. HALLDEN, RAGNHULT & ROOS (1963) and BENTLEY (1964) used interpolation between directly measured dose values in practical and useful systems. The new concept of decrement lines suggested by ORCHARD (1964) may also prove useful in connection with computers in dose planning.

The computer program to be described is based on the same principles as some of the systems mentioned but modifications and expansions have been incorporated according to our needs.

Requirements for a treatment planning program. A computer program must fulfill several requirements to be practical in routine work. These are mainly connected with the fact that most therapy plans can be prepared by hand without too much trouble. This means that a program must be easy to use

Submitted for publication 20 October 1965.

and cheap to run as otherwise no advantage will be gained The amount of data must therefore be cut to a minimum, and the result presented as isodose curves in a directly usable form The program must be able to deal with the most complicated techniques, as for example rotation treatments with correction for lack of tissue and for tissue of density less or greater than one

Method of calculation The basic method of calculation is that suggested by STERLING et coll, although we have had to expand and modify the expressions in several respects in order to cover all our needs reasonably

The calculation of the dose value at a given point in the radiation field may with symmetric fields be separated into three parts (1) calculation of the dose on the central axis at the proper depth, (2) calculation of the decrease in dose due to the distance of the point from the central axis, and (3) correction for surplus of tissue or missing tissue and for air filled tissue

Except in the build up region, the dose on the central axis is assumed to decrease exponentially with depth, with a decay constant depending on the area and perimeter of the field, as found by STERLING et coll To take the build up effect into account an extra empirical term, which vanishes at a depth of a few centimeters, has been included This means that the depth dose D may be calculated according to the following expression

$$D = \exp\,(h + y\,c - 0.0951/(y + 0.6)) \qquad (1)$$

where y is the depth in cm

$$h = 0.125 - 0.0056\,f \qquad (2)$$

$$c = 0.013\,f - 0.083 \qquad (3)$$

$$f = ln\left(\frac{\text{area}}{(\text{perimeter})}\right) \qquad (4)$$

To speed up calculations, the following approximation for the exponential curve has actually been used

$$D = \exp\,(g) \sim \frac{1}{1 + 0.808\,g} + \frac{1.14\,g}{5.19 + g} \qquad (5)$$

where g represents the expression in the parentheses in (1) The maximum discrepancy between (1) and (5) in the interval $0 \leq y \leq 10$ cm is 0.2 % which is unimportant

The profile of the field is assumed to be a cumulative normal distribution function (as suggested by STERLING et coll) except that the dose is corrected for the varying distance from the source on the transversal of the field according to the inverse square law, and for the shielding of the source by the source

holder Both corrections are introduced in the calculations through the empirical correction factor

$$1/[1 + 5\left(\frac{x}{y + SSD}\right)^2]$$

where x is the distance from the central axis

Our cobalt unit (Mobaltron) is supplied with a penumbra trimmer making the edges of the field very sharp near the surface Deeper in the material the dose distribution is more flattened out due to scattering

To include this variation in shape of the field profile it has been necessary to let the standard deviation σ of the normal distribution vary linearly with depth according to the following formula

$$\sigma = 0.005\,y + 0.04 \tag{6}$$

The correction for missing or surplus tissue is obtained by first calculating the extra thickness of tissue d which must be traversed by the radiation on its way from the source to the point where the dose is to be calculated The decrease in the natural logarithm of the dose per cm is c as given by (3) By reducing c for the contribution of the inverse square law at the skin source distance the following correction to g of (5) is obtained at SSD = 80 cm

$$g' = g + (0.0217 + c)\,d \tag{7}$$

By substituting the last y in (1) by $y' = y + d$ the build up correction to the exponential depth dose curve given by the last term in (1) is still applied at the proper place even with correction for extra tissue

The correction for air filled tissue is calculated in a completely analogous way The path through air filled tissue must however be multiplied by one minus the density factor of the light (or heavy) tissue

Only symmetric fields have so far been considered Fields from wedge filters are also included in this analytical representation of radiation fields To ensure that the front lines of the wedge filter isodose curves are straight lines angled e g 45 with the central axis the logarithm of the dose must vary linearly in the direction perpendicular to the central axis as it varies linearly on the central axis This is obtained by including in the bracket in (1) an extra term w

$$w = \frac{\frac{wa}{45}x}{0.39\,y + 10} - (0.053 + 0.031\,a)\left|\frac{wa}{45}\right| \tag{8}$$

where wa is wedge angle in degrees (with sign) and a is the width of the field The denominator of the first term will decrease the angling of the isodose curves with depth as is found by measurement

Table

Example of data for 90 rotation treatment with supporting fixed field — The result is given in Fig 1

```
4 10 1965
[Test on Aldersson phantom section 16]
0       10
0 5      6
3        3
6 5      1
12 5     0
18 2     0 9
23 5     0
29       1
33 6     4
34 7     9
34      13 8
32      18
27      21
21      22 3 fl 80, 12 13 0 270 1 25
15      22 3
9       20 9
4       18 5
1 5     15
—1

1
17 5 4 5 90 9 3 13 0 —4 55 0 1 10 10 90

0
0       1
—1     —1
```

Program details The program is written in ALGOL for the Danish built GIER computer This computer has a 1 024 word fast store and a 12 800 word drum store Program and data are fed into the machine by 8 hole per forated paper tape, and the result is printed on line by means of a fast line printer

Having read the data, the machine sets up a grid covering the area prescribed by the given contour points The distances between grid points are determined by line and character spacing of the line printer, giving a distance in the y direction of 0 84 cm (2 lines) and in the x direction of 1 02 cm (4 characters)

The heart of the program is an ALGOL procedure, which on the basis of field details (entrance point of central axis SSD, width, height wedge angle direction, load factor and contour) will transform grid coordinates into field coordinates, and calculate the dose contribution of a field at all grid points where this contribution is larger than 1 to 2 % of the surface dose

The rest of the program supplies the procedure with the field details both from fixed fields (where they are actually given in the data) and from the single fields of the rotation simulations (where the details must be calculated by the program) Details on the printing are given under the heading results

The program is actually made in three versions of different complexity, and therefore also of different time consumption on the computer The first version will make no corrections for body inhomogeneities or for surplus or missing tissue and will therefore not deal with rotation treatments This version is only used in cases where compensation is used in the treatment The second version is complete except that body inhomogeneities cannot be taken into account which is the case with the third version These versions ensure that computer time is not lost by the use of a too complicated program

Data The data to be used are kept as few as possible to make the program easy to handle An example of the input data for a case using 90 rotation, supported by a fixed field from the front is given in a Table

After the day month and year the calculation may be given a title (name number etc) surrounded by square brackets Then follow in two columns x and y coordinates of points on the contour of the patient The program completes the contour by drawing straight lines between the given points The number of points may be chosen in accordance with the accuracy required and the shape of the contour up to a maximum of 39 If compensation is used in the treatment the patient may often be represented simply by a square box which is then defined complete by just four points

Coordinates should be given in centimeters and are easily read off a piece of millimeter paper on which the contour may possibly be drawn directly

The —1 below the two columns indicates that no more contour points will be given

Fixed fields may then be applied at any given contour point (max number of fields is 5) by supplying seven more numbers after the coordinates of the point The numbers are fixed field number in the case (f1 in the Table), skin source distance (80) field width (12) field height (13) degrees wedge filter (0 for symmetric field) angle between x axis of coordinate system and direction of radiation (270) and load factor (1 25)

The number of different rotation treatments (1 in the Table) must then be given and for each rotation eleven numbers define the treatment *x* and coordinate of rotation axis (17 5 4 5) axis source distance (90) field width (9 3) field height (13) degrees wedge filter (0) angle between source axis direction and radiation direction (—4 55) load factor (0 1) number of fields by which the rotation is simulated (10) angle between these fields (10)

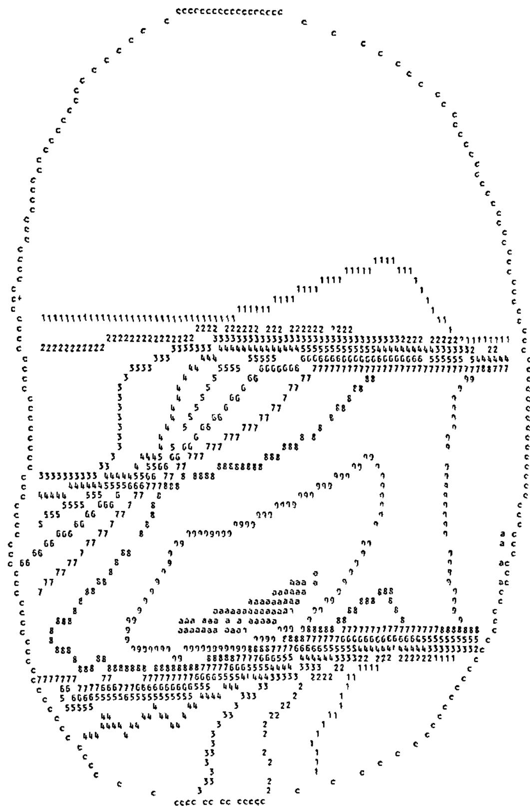


Fig 1 Result of 90° rotation supported by one fixed field from the front (input data as shown in a

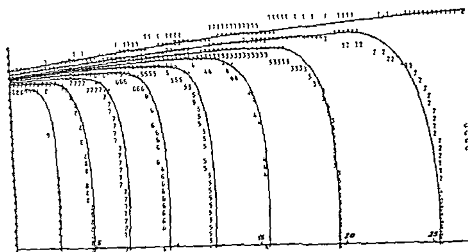


Fig 2 Comparison of calculated and measured isodose curves for a symmetric field of 20 × 10 cm²

angle between x axis and radiation direction of first field (90) There may be a maximum of 3 rotation treatments (with various axes, rotation angles etc) in one calculation

From these numbers the complete rotation is constructed This means that the program itself calculates the entrance points and the skin source distances of the simulating fields

The next zero indicates that no body inhomogeneities are assumed to be present in the actual case

If the lungs are to be taken into account the zero should be changed to two and for each lung a density factor and a lung contour should be given in the same way as the body contour (except that a maximum of 9 points are allowed for each lung)

The numbers that follow specify the form of the result and whether or not more calculations with other fields but the same contour should be performed

Results

When the calculation is finished the result is normalized to 100 % in the maximum point and the normalization factor is printed out

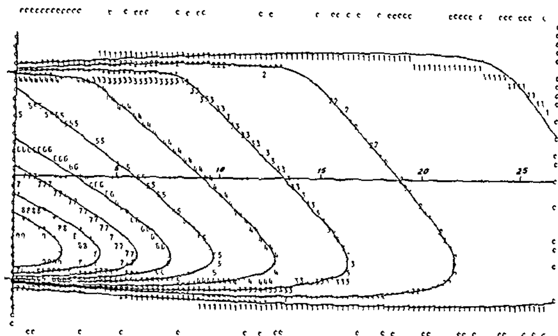


Fig 3 Comparison of calculated and measured isodose curves for a wedge field of 10 × 10 cm²

Dose values at all grid points may be printed out, or, as is normally the case, isodose curves may be printed on the line printer directly (see Fig 1)

The dose between grid points is calculated by linear interpolation

In the result, all the *c* letters symbolize the patient contour and *a* the maximum points An *a* is printed if the dose in the centre of the rectangle (roughly 2 × 4 *mm*²) allocated to a line printer character is ≥ 98 % of maximum

If several isodose curves of the type 70 %, 80 % etc pass through the same rectangle, the figure corresponding to the one which is nearest the dose value at the centre is printed

If no curves of the type 50 %, 60 % etc pass through a rectangle and an isodose curve of the type 45 %, 55 % etc passes through a + will be given Thus, complete isodose curves for 5 %, 15 %, up to 90 % 95 % are printed and give a complete picture of the dose distribution

The printer will supply three copies directly, if these are wanted for different patient files

Discussion

Several different qualities have to be taken into account in any attempt to estimate the value of an automatic dose planning system

First, it is reasonable to make an estimate of the accuracy of the calculations

performed Figs 2 and 3 may give a visual impression From these figures and similar comparisons it is estimated that the discrepancy between measured and calculated dose values of the compared fields are less than 1 % to 2 % of the surface dose except perhaps for some points right on the edges of the fields Here a change in position of a few millimeters which may easily occur during treatment, will however give the same variation in dose

Comparisons have been made with different symmetric fields ranging from 5 × 5 cm² to 20 × 10 cm² and a 45° angle wedge filter (which are the only wedge filters used at this centre) in the range from 6 × 6 cm² to 10 × 10 cm² It is thought that the program will deal also with wedge filters of angles other than 45 but no direct comparisons with measurements have been made

It would appear that the accuracy of the calculations are sufficiently good in relation to the accuracy of the measured isodose curves and the adjustment of fields during patient treatment

Ease of application is also very important in a dose planning system It is felt that the input data should be kept as simple as possible point coordinates rather than angles being used wherever possible as the former appear to be less confusing and therefore safer and quicker

As far as the result is concerned the only possible way of improving this would be the incorporation of a curve plotter preferably on line to avoid delay At this centre a GIER computer run commercially on a service basis, functions with reasonable success The computer is housed about 500 meters from the hospital so that contact is not too difficult If the data tape can be prepared at the hospital it is felt that a more distant computer may be used by means of the normal postal service without excessive delay

As far as the economics of employing a computer in dose planning are concerned this of course completely depends on the price of the computer time and the speed of the program The GIER computer normally costs 12 D Kr/minute and a calculation with three large fixed fields of an extensive area (22 × 35 cm) takes a little less than 2 minutes with the present program A plan containing one fixed field with 90 rotation simulated by 10 fields takes 4 minutes The economics of the system are thus reasonably satisfactory although it might be considerably improved by speeding up the program This may possibly be done as is being attempted at the moment by using simpler functions in the expression of the dose or doubtless by rewriting some of the inner loops of the program in which nearly all the time is spent in machine code

It would appear however that the present form of program is not without value since it handles some of the ordinary routine work and easily manages peak loads which would create difficulties with normal dose planning by hand

Acknowledgement

The author is grateful to C B Madsen for continuous encouragement during the work

SUMMARY

The theory and practical use of a computer program for automatic calculation of isodose curves in cobalt 60 radiation therapy are described The program is based on an analytical representation of radiation fields including those from wedge filters correction being made for patient contour and air filled tissue The result is given directly from the computer as complete isodose curves

ZUSAMMENFASSUNG

Die Theorie und Praxis eines Komputerprogrammes zur automatischen Berechnung von Isodosis Kurven fur Kobalt 60 Strahlentherapie werden besprochen Die Grundlage des Programmes ist die analytische Darstellung der Bestrahlungsfelder einschliesslich der Benutzung von Keilfiltern mit Korrektion fur die Korperform und fur lufthaltiges Gewebe Die Data Maschine gibt die Resultate in Form von vollstandigen Isodosis Kurven

RÉSUMÉ

Description de la théorie et de l emploi pratique d un programme d ordinateur pour le calcul automatique des courbes isodoses en cobalt thérapie Le programme est basé sur une représentation analytique des champs d irradiation y compris l irradiation a travers des filters en coin en faisant les corrections nécessaires pour le contour du patient et les tissus remplis d air Le resultat est fourni directement par l ordinateur sous forme de courbes isodoses complètes

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TRANSFER OF THE NBS ABSOLUTE CALIBRATION FOR MEASUREMENT OF HIGH ENERGY ROENTGEN RADIATION BEAMS

by

R THORAEUS

Units for the production of roentgen radiation of energies much higher than those of the gamma radiation from the commonly used radioactive materials ^{137}Cs ^{60}Co and ^{226}Ra have become available for radiotherapy during the last ten years Linear accelerators betatrons and synchrotrons are well known examples of such units Since such particular characteristics of high energy roentgen and gamma radiation as the skin sparing effect as a function of the build up effect the strongly reduced absorption of energy in bone tissues as compared with that in soft tissues and increased percentage depth doses have proved to be of great clinical value units of the types mentioned have been installed in many radiotherapy clinics

Quantitative measurements of the exposure is however of the same fundamental importance in clinical work with high energy radiation as it is in the employment of low energy radiation When high energy *roentgen radiation*

A brief description of the Swedish measurement equipment was presented at the Meeting of the Nordic Radiophysicists Oslo *13 to 15 September 1963* The material contained in this paper was presented at the *Meeting of the Nordic So iety* of Radiology Helsingfors 4 to 6 June 1964 Submitted for publication 16 August 1965

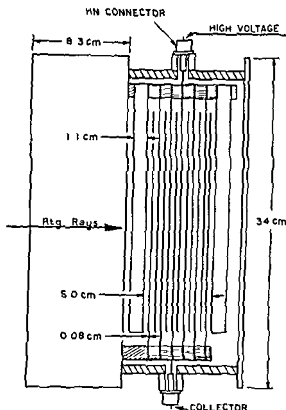


Fig. 1. Schematic cross-section of the NBS 12 chamber. The dimensions given are approximate.

became more commonly available, ordinary thimble ionization chambers were used to indicate the exposure. The chamber was then surrounded by a converter, for example an 11.5 cm lucite cube (ref. 2), and the chamber response was corrected to nominal roentgens with the ^{60}Co calibration factor (ref. 5).

The same method was also used in Sweden at the end of 1957 when the first unit of this type, an 18 MV betatron, was installed at Radiumhemmet. The substandard graphite thimble chamber previously described (ref. 6) was then employed and provided with additional caps of graphite as converters. The ^{60}Co calibration factor of this chamber, provided with a cap of 3.5 mm thick graphite, was originally directly obtained at the NBS in 1956 (ref. 1). The exposure was measured at the centre of beam cross sections, the exposure rate distribution of which was flattened by separate filters as commonly used in radiation therapy. The flattening effect of the filters was checked by photographic films exposed free in air in a position perpendicular to the beam.

This method, however, cannot be universally used. It fails for example in

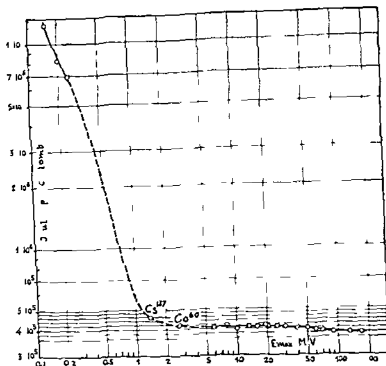


Fig 2 Variation of the NBS P2 chamber calibration factors with maximum photon energy of the beam Because of the absence of calibration results and conditional plotting of Cs and Co gamma radiation the curve drawn is unverified in the gap between 250 kV and 6 MV

the measurement of total beam energy, since the thimble response is generally not proportional to this quantity but rather to the energy incident on a unit area averaged over a limited part of the beam High energy radiation calorimeters were therefore early constructed and used by some institutes in the U S for measurement of the total amount of energy transported by a beam of high energy roentgen radiation Such a calorimeter is however a very complicated instrument which can only be installed at institutes with great resources but even then the long time and particular care required for the measurements preclude its use each time a knowledge of the quantity mentioned is required

It is therefore of great value that the NBS has devoted an extensive research work to the design and construction of a special type of ionization chamber which after an absolute calibration against both a scintillating crystal and a calorimeter enables a convenient determination of the total energy of high energy roentgen beams to be made This type of chamber is labelled P2 and has been described in detail in a paper by PRUITT & DOMEN (ref 3)

Table 1

Elemental composition of the dural alloys used for the NBS and Swedish P2 chambers

Element	NBS chamber		Swedish chambers
	Percentage by weight		Percentage by weight
	Nominal	Limits	Nominal
Aluminium	93.4	90.9—94.7	93.6
Copper	4.5	3.8—4.9	4.4
Magnesium	1.5	1.2—1.8	0.4
Manganese	0.6	0.3—0.9	0.8
Silicon	—	0—0.5	0.8
Iron	—	0—0.5	—
Zinc	—	0—0.25	—
Chromium	—	0—0.1	—
Others	—	0—0.15	—

The constructional principle of the P2 chamber is shown in the schematic drawing in Fig. 1. The chamber is a flat transmission ionization chamber, the size of which is sufficient to intercept the whole beam. The chamber is provided with a suitable wall thickness for the front, which the radiation has to penetrate before it reaches the sensitive volume of dry air in the chamber. The air column is about 5 cm thick and is divided into 12 equal segments. The normally used potential difference between the segment plates is 1 200 V, or about 284 volt per millimetre. These measures effectively contribute to reduce both the solid angle for electron loss and the probability of ion recombination to acceptable levels. All the parts exposed to radiation are made of a dural alloy of specified composition. According to page 1 of ref. 3 the P2 chamber is classified as an NBS Standard instrument particularly useful as a transfer instrument. Its calibration is expressed as the radiation energy in joules required to produce one coulomb of ionization charge inside the chamber when it contains dry air at a temperature of 20° C and a pressure of 760 mm Hg.

One characteristic of the P2 chamber that is of very great interest is the energy dependence of the response. To illustrate this, some of the calibration factors in joules per coulomb given in ref. 3 have been plotted against the maximum photon energy of the beam on the logarithmic diagram shown in Fig. 2. Due to the thickness chosen for the front wall, it was possible to reduce the variation of the calibration factor with the maximum beam energy to 10 per cent between 6 and 170 MV, using a beam filtration equivalent to 4.5

Table 2

Thickness in mm of the discs forming the front wall of the P2-S1 chamber

Number	Thickness	Number	Thickness
1*	11 45	5	11 84
2	11 84	6	11 89
3	11 83	7	11 86
4	11 84	*Sum of 1 to 7*	82 55

* Number 1 is the closing front disc

g/cm² of aluminium and a beam diameter of 4 2 cm at the front face of the chamber The calibration factors of the ^{137}Cs and ^{60}Co gamma radiations were plotted against 1 4 and 2 8 MV, approximately corresponding to the maximum energies of roentgen radiation having the same first HVL as the respective gamma radiation It appears from the diagram that the calibration factors in the region 150 to 250 kV are approximately 30 to 17 5 times greater than those in the 6 to 170 MV region which in a high degree depends on the increased attenuation of the radiation in the thick front wall

The diagram in Fig 2 only generally shows the energy dependence and may therefore not be used to read or interpolate calibration factors Experimentally determined factors are for example not available in the wide region between ^{137}Cs gamma and 250 kV roentgen radiation and the factors of ^{60}Co and ^{137}Cs gamma radiation are conditionally plotted The curve drawn is therefore unverified in this region

The features of the P2 chamber mentioned above together with other interesting properties experimentally verified in ref 3 indicate that this chamber is a perfectly good and very convenient instrument for the purpose in question and that its design is such that a reproduction elsewhere would be feasible provided each important detail be carefully controlled It was therefore decided in 1962 to start a project aiming at a transfer of the NBS absolute calibration of the P2 chamber for determination of the total energy transported by high energy roentgen radiation beams by producing three identical P2 replica chambers for this institute one to be kept by the standard laboratory one by the clinical radiophysics section and one by the roentgen inspection section

According to ref 4 page 107 such a procedure would eliminate the need to reproduce the original calibration experiments A laboratory with a calibrated replica chamber has the information required to make its own absolute determination of the radiation energy incident on experimental

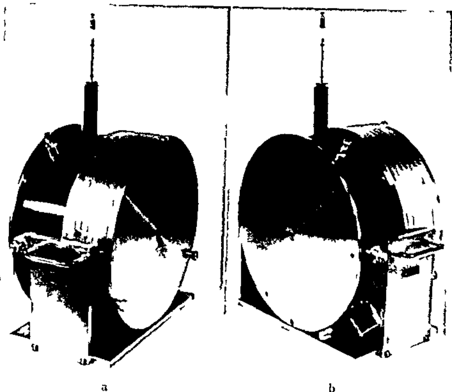


Fig 3 Photographs of front (a) and rear surface (b) of the Swedish P2 S1 replica chamber

apparatus, a number required for quantitative interpretation of experimental results

The project was facilitated by the release of copies of drawings and specifications from NBS Washington and by their kind loan of an NBS chamber for the purpose of comparison

A brief report showing the results of our efforts to realize the project and of the comparison between the NBS P2 3 and our chamber P2 S1 is given below The last mentioned chamber will be kept by the standard laboratory of this institute

To ensure that the Swedish chambers would be as exact copies of the NBS P2 chamber as possible it was fundamentally important to use a material of very nearly the same composition of elements and thickness for all the parts exposed to radiation Some difficulties were encountered but after much search such a material was found The composition of the material used for the Swedish chambers is shown in Table 1 together with that of the material used for the NBS chambers quoted from ref 3 for comparison As the two materials are very similar in composition they may be compared by calculating their

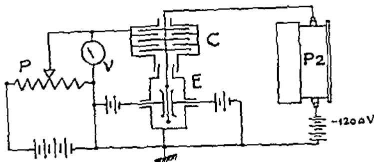


Fig 4 Charge-collecting capacitor with compensating arrangement for charge measurement C—charge collecting capacitor E—single string electrometer used as null-condition indicator P—potentiometer and V—precision voltmeter

average atomic numbers from the atomic numbers and nominal percentages by weight of the ingredients as given in Table 1 We then obtain 13 775 for the NBS dural and 13 796 for the Swedish The density of our material was extensively checked by the dimensions and weights of the different parts, and was found to be 2 795 for the stack plates and 2 796 for the front wall plates This may be compared with 2 790 for the material of the NBS P2 3 chamber

The internal plate assembly defining the sensitive volume where ionization is produced and collected contains dry air at atmospheric pressure This air gap is divided into 12 equal segments by thin dural plates to reduce the probability of ion recombination These plates are 0 788 ± 0 012 mm thick which may be compared with 0 795 ± 0 007 mm as specified in the chamber drawings They are separated by ground steel spacers the average thickness of which is 9 269 ± 0 007 mm this value was calculated as the average of all the readings taken at two opposite positions of each spacer, and may be compared with 9 261 ± 0 007 mm as specified in the chamber drawings

From the figures given above we are able to calculate the thickness of the air gap We then obtain 6(9 269—0 788) = 50 886 mm for the Swedish chamber and 6(9 261—0 795) = 50 796 mm from the chamber drawings According to Table 8 in ref 3 the actual air gap thickness of the NBS P2 3 chamber is 50 69 mm The two thick outer plates of the high voltage stack enclosing the air gap are 11 41 ± 0 02 mm thick which may be compared with 11 43 ± 0 05 mm as specified in the chamber drawings

The plates enclosing the air gap segments consist of high voltage (—1 200 V from a battery power supply) plates alternating with collector plates Each plate stack is separately mounted with high grade insulators on the grounded

front wall of the chamber The whole plate structure is housed in a cylindrical brass shell the ends of which are closed with dural walls

The front wall of our chamber P2 S1 consists of seven discs the thickness of which are shown in Table 2 No 1 is the closing disc the thickness of which 11 45 ± 0 03 mm, may be compared with 11 43 ± 0 05 mm as specified in the chamber drawings The thickness of the seven discs together is 82 55 mm and is the same as that specified in the drawings The rear wall of the chamber is 6 38 ± 0 02 mm thick, which may be compared with 6 35 mm as specified in the chamber drawings

Two photographs of the Swedish chamber P2 S1 are shown in Fig 3 The weight of each chamber is about 40 kg which makes them reasonably portable

The charge collected from the P2 chambers was determined by a compensating arrangement of the type shown in Fig 4 The charge was collected by a high grade insulation capacitor, across which an increasing voltage was then developed This voltage was cancelled by that supplied by a potentiometer and measured by a precision voltmeter The null condition was indicated by a single string electrometer adjusted to high sensitivity The capacitors used were calibrated against the standard air capacitor mentioned on page 208 of ref 7 and having a capacitance of 204 3 $\mu\mu F$ ± 0 1 per cent The compensating voltage was continuously adjusted during each exposure to maintain the electrometer string as near as possible at ground potential

When beams of gamma and high energy roentgen radiation are to be measured, leakage and stray radiation (back ground) cannot be completely eliminated The air volume of the P2 chamber exposed to such radiation is however, of the order of 50 times greater than that exposed to the beam It was therefore considered necessary to correct the reading of the charge produced by the beam by that produced by the background This correction was obtained by repeating the exposure with the collimating opening closed by a full length well fitting lead plug

The comparison program was originally planned to be carried out up to about 18 MV by the present betatron at Radiumhemmet and to be extended up to about 40 MV by a new betatron at Radiumhemmet For various reasons however, the installation of this unit has been very much delayed In the meantime, a 42 MV betatron had been ordered for the radiotherapy clinic of the Regional Hospital at Orebro and was expected to be ready for operation at the end of 1964 It was therefore decided to inquire of the NBS about the feasibility of extending the time of keeping the P2 3 chamber so as to include that required for this purpose Fortunately, there had been no request for P2 chambers so the NBS kindly consented to meet our wish Due to this and to the friendly cooperation of K J VIKTERLOF, Chief Hospital Physicist of the

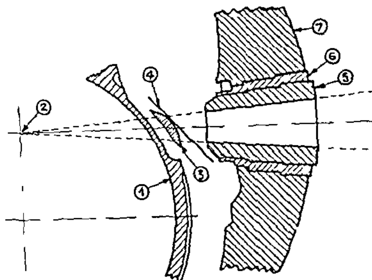


Fig 5 Schematic section of the 18 MV betatron head showing roentgen radiation beam exit 1—donut wall 2—focus 3—position of flattening filter when such a one is used 4—mirror of beam simulating light system 5—collimator 6—collimator holder 7—main lead shield of betatron head

Regional Hospital at Orebro the comparison was extended to include 25 and 42 MV

The comparison of the response to roentgen radiation was made by measuring the charge collected from each chamber when they were given identical radiation exposures as referred to equal readings of a separate monitoring integrating instrument This instrument was at first compared with the P2 S1 using a moderately filtered 250 kV roentgen beam having a HVL of 17 5 mm Al The P2 S1 chamber was then only provided with the closing front plate No 1 The focal distance to this front plate was about 2 metres and the beam diameter at this distance about 65 mm Twelve consecutive exposures were made each of 1 50 min duration and all of them within an operating period of about 45 min and the P2 S1 reading in volt per 100 monitor scale divisions were calculated The ratios thus obtained were in order as follows 98 5 98 3 98 3 98 4 98 5, 98 4 98 5 98 5 98 6 98 5 98 6 98 5 averaging 98 47 ± 0 15 per cent and thus showing satisfactory agreement The response of the P2 S1 chamber with only the closing front plate No 1 was 7 562 times greater than that with all the front plates A similar series comparing the monitoring instrument with the P2 3 and comprising 6 consecutive exposures was later obtained by the 42 MV roentgen beam of the Orebro betatron and gave the following

Table 3

Results of the comparison — Average ionization ratio 0.996 ± 0.2 per cent

Radiation	HVL mm Al		Focal distance in m to chamber face	Beam cross section in mm at chamber face	Ionization ratio P2 3 / P2 S1
	First	Second			
150 kV roentgen	10.7	11.5	2	42 Ø	0.994
200 kV »	13.6	14.8	2	42 Ø	0.995
250 kV »	15.9	16.8	2	42 Ø	0.997
400 kVp »	19.3	19.8	1	42 Ø	0.994
^{137}Cs gamma	34.5	34.5	1	~65 Ø	0.996
^{60}Co »	46.5	46.5	1	~65 Ø	0.995
7 MV roentgen	Inherent filtration		1	45 Ø	0.995
16.5 MV »	3.3 g/cm²		1	45 Ø	0.998
25 MV »	Inherent filtration		1.5	50 × 50	0.995
42 MV »	3.8 g/cm²		1.5	50 × 50	0.996

values of volt per 100 monitor scale divisions 166.9, 166.9, 166.7, 166.6, 166.7, and 166.8, averaging 166.8 ± 0.1 per cent

The final step in the comparison procedure was then to study the ionization charge collected by the P2 3 and P2 S1 chambers referred to equal readings of the monitor instrument. This was carried out over a wide range of radiation qualities, using moderately filtered roentgen beams of 150, 200, and 250 kV constant potential and 400 kVp, gamma beams from ^{137}Cs and ^{60}Co, and finally roentgen beams of 7, 16.5, 25 and 42 MV. The quality of the six first mentioned beams may be characterized by their half value layers, the first and second being experimentally determined.

The inherent filtration of the 18 MV betatron at Radiumhemmet may be defined as follows. The accelerator tube (donut) is made of a ceramic material, the density of which is 2.6. The donut wall, through which the beam is emitted, is 10 to 12 mm thick. In addition the beam passes through a glass mirror about 1 mm thick and belonging to the beam simulating light system. This means a total of about 3.3 g/cm² of low atomic number material similar to aluminium. No flattening filter was used. Fig. 5 shows a schematic section of the 18 MV betatron head at the roentgen radiation beam exit.

The donut of the Örebro 42 MV betatron is also made of a ceramic material the density of which is 2.35. The donut wall, through which the beam is

emitted, is 15 mm thick In addition the beam passes through a glass mirror about 1 mm thick belonging to the beam simulating light system This means a total inherent filtration of about 3 8 g/cm² of low atomic number material similar to aluminium No flattening filter was used

Systematic errors in the comparison were reduced as much as possible by using the same arrangement for placing the two P2 chambers in identical positions in each beam and the same measuring equipment with both of them Each value of the ionization charge collected was obtained as the average of at least three consecutive readings

The ionization ratio $\frac{\text{P2 3}}{\text{P2 S1}}$ and some other relevant experimental data have been collected in Table 3 It appears that the ionization ratio does not show any trend of systematic variation Calculation of the average ratio may therefore be justified and gives 0 996 ± 0 2 per cent

The results obtained with P2 S1 verifies that the design of the P2 chamber is such that a reproduction is quite feasible if the important details are carefully controlled with special regard to material and dimensions The problem most difficult to solve seems to be that of finding a dural alloy of very nearly the same elemental composition as that used for the original P2 chambers However if such a material is available the reproduction is mainly a question of accurate machining by which the various parts are given the proper dimensions within the requisite narrow limits It appears from the results now reported that we have been able to transfer the NBS absolute calibration of the P2 chamber to this laboratory with acceptable accuracy

Acknowledgements

The author wishes to express his sincere thanks to the NBS and to J S Pruitt and H O Wyckoff in particular for releasing the NBS drawings and specifications and lending us one of the NBS chambers for comparison to K J Vikterlof for his friendly cooperation and to the Anti Cancer Society of Stockholm for defraying the expenses for two of the chambers This report and the results of the comparison are published with due permission of the NBS

SUMMARY

Three identical ionization chambers of the special type developed by the NBS and labelled P2 have been constructed to transfer the NBS absolute calibration for *determination of the* total amount of energy transported by high-energy roentgen radiation beams Some characteristics of the Swedish replica chambers are discussed

ZUSAMMENFASSUNG

Drei identische Ionisationskammern vom Typ NBS, Modell P2, wurden gebaut um die absolute NBS Eichung zur Bestimmung der von hochenergetischen Röntgenstrahlbündeln transportierten totalen Energie zu überführen Einige charakteristische Angaben der schwedischen Kammern werden besprochen

RÉSUMÉ

Trois chambres d ionisation identiques du type spécial mis au point par le NBS et appelé P2 ont été construites pour transférer l étalonnage absolu du NBS en vue de déterminer la quantité totale d énergie transporté par des faisceaux de rayonnement roentgen de haute énergie L auteur examine certaines caractéristiques de ces chambres répliques suédoises

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FROM THE PHYSICS DEPARTMENT OF THE INSTITUTE OF ONCOLOGY (DIRECTOR JEREMI SWIECKI), GLIWICE, POLAND

INFLUENCE OF TRANSVERSE DIMENSIONS OF BONE ON ROENTGEN DOSE DISTRIBUTION FOR DIFFERENT QUALITIES OF PRIMARY RADIATION

by

WLODZIMIERZ LOBODZIEC and BARBARA LUBAS

Tumours subjected to roentgen therapy are often screened by bone Changes in the depth dose distribution under bone beyond the range of secondary electrons produced in the bone by absorption of radiation may be of importance from the treatment viewpoint This matter has been elaborated previously when the absorption of roentgen radiation in bone was discussed The authors now present their investigation on the dose distribution for different qualities of primary radiation dependent on the transverse dimensions of bone

The radiation at any point in an absorbing medium consists of two components (1) the primary radiation attenuated in the medium and (2) the radiation scattered in the medium which among other factors depends on the area of the field irradiated the quality of the primary radiation and the parameters of the scattering medium

The attenuating medium is usually not homogenous in practice but in this

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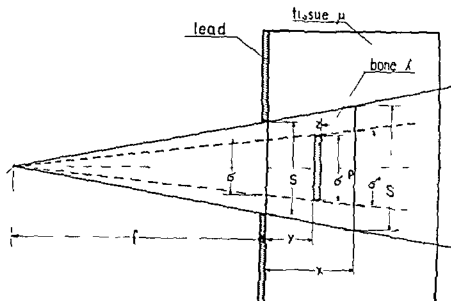


Fig 1 Model of an unhomogenous medium

paper a simplification only of the non homogeneity will be considered The media investigated consist of soft tissue (linear attenuation coefficient μ) and bone (linear attenuation coefficient λ)

Let us consider the dose rate at a certain point P on the central axis of a roentgen beam of cross section S at a fixed source surface distance (SSD) f, and situated at depth x in an irradiated medium of linear attenuation coefficient μ (Fig 1)

Assuming that the primary radiation gives the dose rate D_0 at distance f from the source of radiation, the dose rate will increase at the surface s of the medium irradiated according to the following equation

$$D_S = B_S D_0, \tag{1}$$

where B_S is the back scatter factor at the surface dependent inter alia on the dimensions of the field irradiated and the quality of primary radiation

If the linear attenuation coefficient of the beam in the medium is μ, then the quantity expressed by eq (1) will have the following value on the central axis at depth x

$$D_S^{(x)} = \left(\frac{f}{f+x}\right)^2 B_S^{(x)} D_0 e^{-\mu x} \tag{2}$$

where $B_S^{(x)}$ is the scatter factor at depth x in the medium of linear attenua

tion coefficient μ for the area S of the irradiated field At depth x, the cross section of the beam will be

$$S = s\left(\frac{f+x}{f}\right)^2 \tag{3}$$

The scatter factor $B_S^{(x)}$ is defined as

$$B_S^{(x)} = \frac{D_S^{(x)}}{D_{S=0}^{(x)}} \tag{4}$$

Factor $e^{-\mu x}$ in eq (2) characterizes the exponential attenuation with depth of the primary radiation in the medium irradiated Factor $B_S^{(x)}$ is the only responsible for the variation with depth of the scattered radiation

If bone of thickness ϵ, cross section $\sigma < S$ and linear attenuation coefficient λ is present in the medium of soft tissue between point P and the surface to be irradiated at depth y (see Fig 1), the projection of σ on the area S at depth x will be

$$\sigma_x = \sigma\left(\frac{f+x}{f+y}\right)^2 \tag{5}$$

and at the irradiated surface

$$\sigma_0 = \sigma\left(\frac{f}{f+y}\right)^2 \tag{6}$$

According to the explanations presented the dose rate at point P may be expressed as the sum of two components

$$D_S^{(x)} = D_{S-\sigma}^{(x)} + D_\sigma^{(x)} \tag{7}$$

The first of these components $D_{S-\sigma}^{(x)}$ indicates the dose rate for a beam (a) at the surface covering an area $(S-\sigma)$ and consequently at depth x an area $(S-\sigma_x)$ (b) that would be attenuated only in the medium of soft tissue of thickness x

The scatter factor $B_{S-\sigma}^{(x)}$ at depth x for the area $(S-\sigma)$ at the surface is the difference between the scatter factors at this depth for the irradiated fields S and σ

$$B_{S-\sigma}^{(x)} = B_S^{(x)} - B_\sigma^{(x)} \tag{8}$$

so the dose rate $D^{(x)}_{S-\sigma}$ after taking into consideration eqs (2) and (8) may be expressed as

$$D^{(x)}_{S-\sigma} = \left[B^{(x)}_{S} - B^{(x)}_{\sigma}\right]\left(\frac{f}{f+x}\right)^2 D_0 e^{-\mu x} \tag{9}$$

The second of the components in eq (7), $D^{(x)}_{\sigma}$, represents the dose rate at depth x from a radiation beam that (a) would cover an irradiated surface area of σ and at the depth x an area of σ, and (b) would be attenuated in medium of soft tissue of thickness $(x-z)$ and in bone of thickness z.

The scatter factor at depth x for the area σ at the surface is expressed as $B^{(x)}_{\sigma}$, and the factor of exponential attenuation in this case will be $e^{-\mu(x-z)}\, e^{-\lambda z} = e^{-[\mu(x-z)+\lambda z]}$, so the dose rate $D^{(x)}_{\sigma}$ may be expressed as

$$D^{(x)}_{\sigma} = B^{(x)}_{\sigma}\left(\frac{f}{f+x}\right)^2 D_0 e^{-[\mu(x-z)+\lambda z]} \tag{10}$$

Consideration has not been given in eqs (7) to (10) to the dependence of the scatter factors

$$B^{(x)}_{S-\sigma} = \frac{D^{(x)}_{S-\sigma}}{D^{(x)}_{S-\sigma-0}} \quad \text{and} \quad B^{(x)}_{\sigma} = \frac{D^{(x)}_{\sigma}}{D^{(x)}_{\sigma-0}}$$

on the presence or absence of bone, nor to the influence of radiation scattered bone on the dose rate at point P.

Independence of the presence or absence of bone for the scatter factors considered was experimentally verified. It was proved that absorption in bone (of 3 cm maximal thickness) of low energy scatter radiation may change the scatter factors to limits close to the experimental error. The maximum difference observed between the scatter factors, as depending on the presence or absence of bone, was 8 % for primary radiation of the lowest effective energy 47 kV.

The influence of the radiation scattered in the bone may be neglected because our considerations are related to points beyond the range of secondary electrons produced by absorption of roentgen radiation in bone. This also was verified experimentally.

After transformation of eq (9) and adding it to eq (10) the following equation is obtained

$$D^{(x)}_{S} = \left(\frac{f}{f+x}\right)^2 D_0 e^{-\mu x}\left[B^{(x)}_{S} - B^{(x)}_{\sigma}\left(1 - e^{-(\lambda-\mu)z}\right)\right] \tag{11}$$

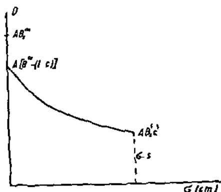


Fig 2 Influence of the transverse dimensions of bone on the dose distribution when the parameter c is fixed

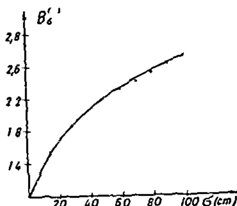


Fig 3 Scatter factor as a function of the irradiated field area at 10 cm depth for SSD 40 cm and HVL 1 5 cm C

With z = const we obtain

$$e^{-(\lambda-\mu)z} = c = \text{const} < 1 \tag{12}$$

When x is fixed the factor $\left(\frac{f}{f+x}\right)$ $D_0 e^{-\mu x} = A$ = constant also

According to these conditions eq (11) may be expressed in the final form

$$D_s' = A\left[B_s^{(\cdot)} - B^{(\cdot)}(1-c)\right] \tag{13}$$

giving the influence of the transverse dimensions of bone of linear attenuation coefficient λ on the dose rate at point P

The independent variable σ in eq (13) is contained in the factor $B^{(\cdot)}$ which is a function of σ

The value of D_s as a function of the independent variable σ may be derived from a previous experimental determination of the factor $B^{(\cdot)}$ for different sigmas if the parameter c is fixed

The graphical analysis of eq (13) is presented in Fig 2 In the absence of bone (z = 0) eq (13) is represented in the graph by point $D_s^{(\cdot)} = A\ B_s'$ If bone of thickness z but of transverse dimensions decreasing to zero is present in the medium of soft tissue then

$$D_s = A\left[B_s^{(\cdot)} - (1-c)\right]$$

The exponential attenuation of roentgen radiation in bone of thickness z

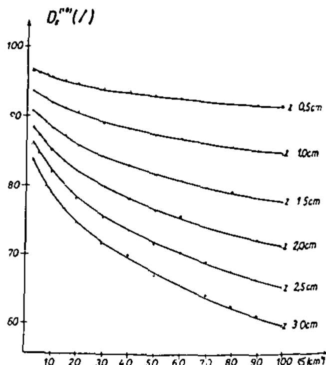


Fig. 4. Decrease of percentage dose below bone as a function of the increase in cross section σ at different thicknesses z (area of irradiated field 100 cm²)

is responsible for the decrease in dose rate from points $1B_S^{(\ )}$ to point $1[B_S^{(\ )}-(1-c)]$. Only the transverse dimensions of bone accounted for the further diminution of the dose rate at points under bone along the curve (for a given quality of radiation and fixed thickness z). The shape of the curve will

Table

Depth scatter factors $B_S^{(\ )}$ or $B_\sigma^{(\ )}$ for qualities of primary radiation of HVL 0.5 to 3.0 mm Cu SSD 50 cm

S or σ (cm²)	At 3 cm depth HVL mm Cu					At 5 cm depth HVL mm Cu				
	0.5	1.0	1.5	2.0	3.0	0.5	1.0	1.5	2.0	3.0
4	1.37	1.33	1.28	1.23	1.16	1.33	1.31	1.29	1.25	1.1[illegible]
10	1.60	1.52	1.45	1.42	1.33	1.63	1.60	1.56	1.51	1.43
15	1.67	1.63	1.59	1.52	1.43	1.85	1.78	1.71	1.63	1.55
20	1.78	1.72	1.66	1.59	1.49	2.00	1.92	1.81	1.72	1.63
30	1.95	1.86	1.77	1.64	1.575	2.22	2.11	1.97	1.87	1.76
50	2.14	2.05	1.95	1.83	1.70	[illegible]	2.40	2.23	2.10	1.93
75	2.29	2.21	2.08	1.96	1.795	2.78	2.66	2.44	2.28	2.08
100	2.38	2.32	2.170	2.05	1.865	[illegible]	2.82	[illegible]	2.42	2.19
150	2.53	2.44	2.30	2.17	[illegible]	3.18	3.05	2.79	2.61	2.32
200	2.59	2.53	2.39	2.24	2.03	3.32	3.18	2.93	2.75	2.44

be retained for different parameters of c due to the monotony of the function $B^{(\,)} = B(\sigma)$ The inclination of this curve to the axis of the abscissa will however be smaller or greater in relation to the value of the parameter c (with increase in c, this inclination decreases)

Application of theory to given quality of primary radiation

With a view to exemplify the application of the method in the evaluation of the influence of the transverse dimensions of bone on the dose distribution below bone measurements and calculations were carried out, using a radiation quality of HVL 1 5 mm Cu effective wave length 0 13 Å

The factors $B_S^{(\,)}$ or $B^{(\,)}$ eq (4) were determined in a presdwood phantom at depth $x = 10$ cm measured from the phantom surface The irradiation was performed by means of closed end applicator SSD 40 cm the area of fields irradiated being squares of dimensions varying between 2 5 cm² and 100 cm² The dose rates were measured by means of Victoreen thimble ionization chambers

The results of the measurements are presented in Fig 3 In the present charts *the maximum percentage error involved amounted to about* 8 % for the small areas but for the majority of points the error was less than 5 %

On the basis of eq (13) and the results shown in Fig 3 curves representing *the dose distribution below* bone were constructed as dependent on the transverse dimensions of the bone at roentgen radiation with HVL 1 5 mm Cu

Table *(cont)*

At 8 cm depth HVL mm Cu					At 12 cm depth HVL mm				
0 5	1 0	1 5	2 0	3 0	0	1 0	1 5	2 0	3 0
1 50	1 42	1 37	1 30	1 21	1 56	1 44	1 33	1 25	1 0
1 90	1 80	1 69	1 63	1 49	2 23	1 94	1 84	1 70	1 61
2 10	2 01	1 98	1 81	1 65	2 44	2 24	2 12	2 00	1 80
2 3	2 18	2 05	1 94	1 6	2 74	2 48	2 34	2 22	1 96
2 65	2 46	2 9	2 16	1 93	3 25	2 84	2 66	2 51	2 20
3 07	2 83	2 65	2 50	2 21	3 93	3 43	3 19	2 97	2 57
3 45	3 19	2 99	2 8	2 47	4 51	3 39	3 71	3 44	2 91
3 73	3 47	3 2	3 00	2 65	4 89	4 43	4 12	3 80	3 20
4 13	3 86	3 59	3 32	2 80	5 0	5 08	4 75	4 39	3 62
4 45	4 17	3 84	3 55	3 08	6 25	5 53	5 16	4 76	3 93

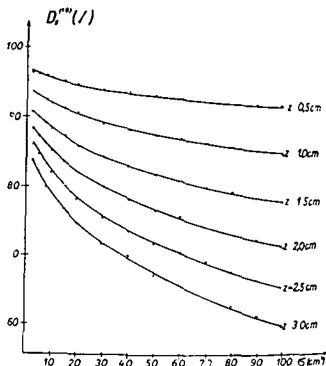


Fig 4 Decrease of percentage dose below bone as a function of the increase in cross section σ at different thicknesses z (area of irradiated field 100 cm²)

is responsible for the decrease in dose rate from points $1B_s^{()}$ to point $1\left[B_s^{()}-(1-c)\right]$ Only the transverse dimensions of bone accounted for the further *diminution of the dose rate at points under bone along the curve* (for a given quality of radiation and fixed thickness z) The shape of the curve will

Table

Depth scatter factors $B_S^{()}$ or $B_\sigma^{()}$ for qualities of primary radiation of HVL 0 5 to 3 0 mm Cu SSD 50 cm

S or σ (cm²)	At 3 cm depth HVL mm Cu					At 5 cm depth HVL mm Cu				
	0 5	1 0	1 5	2 0	3 0	0 5	1 0	1 5	2 0	3 0
4	1 37	1 33	1 28	1 23	1 16	1 33	1 31	1 29	1 25	1 19
10	1 60	1 52	1 45	1 42	1 33	1 63	1 60	1 56	1 51	1 43
15	1 67	1 63	1 59	1 52	1 43	1 85	1 78	1 71	1 63	1 55
20	1 78	1 72	1 66	1 59	1 49	2 00	1 92	1 81	1 72	1 63
30	1 95	1 86	1 77	1 64	1 575	2 22	2 11	1 97	1 87	1 76
50	2 14	2 05	1 95	1 83	1 70	2 59	2 40	2 23	2 10	1 93
75	2 29	2 21	2 08	1 96	1 795	2 78	2 66	2 44	2 28	2 08
100	2 38	2 32	2 170	2 05	1 865	2 95	2 82	2 60	2 42	2 19
150	2 53	2 44	2 30	2 17	1 9[illegible]	3 18	3 0	2 79	2 61	2 32
200	2 59	2 53	2 39	2 24	2 03	3 39	3 18	2 93	2 75	2 44

2 Interpolate the values of linear attenuation coefficients λ and μ for the given HVL of the radiation used and calculate the values of parameter $c = e^{-(\lambda-\mu)}$

3 Determine the value $1 = \left(\frac{f}{f+x}\right)^2 D_0 e^{-\mu}$ for x which is the depth of the selected point at the central axis of the roentgen beam

4 Calculate or evaluate according to formula (6) the value σ of the area of projection of σ on the surface irradiated under certain conditions of irradiation in using a large SSD and for small depths of y and x, the values σ σ and σ may be approximated to one another

5 Calculate or interpolate from depth dose tables the values of the scatter factors $B^{()}$ for the value σ and $B^{()}$ for the area S of the field irradiated

6 Calculate value $D_s^{(}$ using formula (13) and divide it by $1B_c^{()}$ then the *percentage transmission of radiation throughout the bone analogous to that* presented in the graphs of Fig 4 may be obtained

This procedure enables a decision to be taken as to whether the influence of a given bone is so small as to be neglected or is of such size as to be considered

Acknowledgements

The authors wish to thank Mrs Lucyna Tyrala for her help with the calculations and for preparing the graphs

SUMMARY

The influence of the transverse dimensions of bone on the roentgen dose distribution at points situated below the bone is discussed The problem is theoretically elaborated and the application of the theory to different qualities of radiation and dimensions of bone is described

ZUSAMMENFASSUNG

Es wird erortet in wie weit die Dicke des Knochens die Rontgendosis Verteilung in darunter liegenden Teilen beeinflusst Nach einer Besprechung der theoretischen Unterlagen werden die praktischen Verhaltnisse unter Berucksichtigung verschiedener Strahlenqualitaten und Knochendicken erlautert

RÉSUMÉ

Les auteurs etudient l influence des dimensions transversales de l os sur la distribution de doses en points situes au dessous de cet os Ils étudient ce probleme théoriquement et decrivent l application de la théorie pour différentes qualités de rayonnement et differentes dimensions d os

of a field 10 cm × 10 cm in a chosen region of bone thickness 0.5 cm ⩽ z ⩽ 3 cm. For this quality of radiation (data from SPIERS) the linear attenuation coefficient of bone, λ, is 0.319 cm^{-1}, and of soft tissue, μ, = 0.175 cm^{-1}.

The curves displayed in Fig. 4 refer to different thicknesses, z, of bone but to a dose distribution at the same depth of 10 cm.

The measurements and calculations performed permit the conclusion to be drawn that under constant conditions as regards SSD, area of field irradiated and quality of primary radiation the depth dose under bone decreases with increasing transverse dimensions of the bone, and the thicker the bone the more marked the reduction in depth dose.

Application of theory to different qualities of primary radiation

The dependence of the depth dose distribution below bone on the transverse dimensions of the bone at different depths and different qualities of primary radiation may be calculated from published depth dose tables (see reference to Brit. J. Radiol. Suppl. 10, 1961). The depth dose $D_S^{(x)}$ may be calculated from such tables by multiplying the percentage dose at depth x by the back scatter factor for the area S of the irradiated field. (The values of the back scatter factors may be found from the same tables.)

The scatter factors $B_S^{(x)}$ for limited diaphragm areas S of square fields, or $B_\sigma^{(x)}$ for areas σ at different qualities of radiation and at different depths x under the irradiated surface may be calculated according to the formula (4) as follows

$$B_S^{(x)} = \frac{D_S^{(x)}}{D_{S0}^{(x)}} \text{ or } B_\sigma^{(x)} = \frac{D_\sigma^{(x)}}{D_0^{(x)}}$$

The graphs $B_S^{(x)}$ versus S may then be drawn and from these graphs $B_S^{(x)}$ for any field and depth may be read.

The value of parameter $c = e^{(\lambda-\mu)}$ for a chosen quality of primary radiation and bone thickness may be calculated after interpolation of the values of the linear attenuation coefficients λ for bone and μ for soft tissue from the data given by SPIERS.

Such calculations may be applied in roentgen therapy for any dimensions of bone and for any combination of tumour site and screening bone according to the following steps:

1. Evaluate the average thickness, z, the cross section, σ, and the depth y, of the bone screening the irradiated tumour.

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RETENTION OF STRONTIUM 85 IN RATS

III Effect of increasing the doses of sodium and barium sulphates and role of the time factor

by

VLADIMIR VOLF and ZDENEK ROTH

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Method and Material Details of the procedure have been described previously (VOLF & ROTH 1965) Fasting male Wistar albino rats were given single doses of ^{85}Sr chloride (1 to 2 μCi) and sulphates in distilled water by means of a stomach tube Whole body and skeletal retention of ^{85}Sr were determined and expressed as percentages of the dose administered (For detailed information regarding computation and testing of regression lines, see Appendix)

One hundred and sixty nine rats weighing from 170 to 190 g were used when increasing the doses Sulphates were administered 10 min after the ^{85}Sr

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RETENTION OF STRONTIUM 85 IN RATS

III Effect of increasing the doses of sodium and barium sulphates and role of the time factor

by

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One hundred and sixty nine rats weighing from 170 to 190 g were used when increasing the doses Sulphates were administered 10 min after the ^{85}Sr

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Table 1

Effect of increasing doses of sulphates given orally 10 min after oral contamination with ^{85}Sr

Substances tested	Dose (mM)	Number of animals	Percentage of ^{85}Sr administered					
			Whole body				Skeleton[1]	
			After 24 hours		After 48 hours		After 48 hours	
			$\bar{x} \pm ts_{\bar{x}}$[2]	Percentage of control	$\bar{x} \pm ts_{\bar{x}}$	Percentage of control	$\bar{x} \pm ts_{\bar{x}}$	Percentage of control
Na_2SO_4	Controls	6	49 4 ± 19 7	100	35 0 ± 11 3	100	25 0 ± 9 9	100
	0 2	6	40 9 ± 7 3	n s[3]	25 3 ± 3 5	n s	19 5 ± 3 9	n s
	0 4	6	34 0 ± 7 6	n s	23 7 ± 4 4	n s	18 8 ± 1 4	n s
	0 8	6	32 2 ± 7 6	n s	20 0 ± 5 3	57	15 [illegible] ± [illegible]4	61
Na_2SO_4	Controls	6	41 2 ± 12 6	100	31 9 ± 8 9	100	23 6 ± 5 4	100
	0 8	5	31 5 ± 8 7	n s	20 9 ± 8 4	65	13 9 ± 7 8	59
	1 6	5	22 3 ± 12 3	54	14 9 ± 7 1	47	9 5 ± 5 7	40
	2 4	5	37 1 ± 12 3	n s	19 7 ± 5 9	63	11 5 ± 4 1	4[illegible]
	3 2	5	35 0 ± 18 4	n s	18 5 ± 8 6	58	9 6 ± 4 0	41
$BaSO_4$I	Controls	6	44 3 ± 11 4	100	31 6 ± 6 2	100	24 9 ± 6 [illegible]	100
	0 2	6	26 0 ± 7 3	59	19 8 ± 4 7	63	15 4 ± 5 0	6[illegible]
	0 4	6	25 0 ± 5 7	56	16 3 ± 4 6	52	11 9 ± 4 0	48
	0 8	6	21 2 ± 19 3	48	8 1 ± 4 3	25	5 2 ± 3 0	21
$BaSO_4$II	Controls	6	35 8 ± 8 8	100	27 2 ± 7 8	100	23 6 ± 7 3	100
	0 8	6	35 4 ± 21 1	n s	20 0 ± 5 4	n s	18 5 ± 3 4	n s
	1 6	6	23 1 ± 4 8	65	17 6 ± 4 6	65	15 8 ± 4 7	n s
	3 2	6	18 2 ± 6 3	51	12 8 ± 5 4	47	12 1 ± 6 0	51
$BaSO_4$III	Controls	6	38 7 ± 11 4	100	26 9 ± 5 1	100	24 4 ± 4 8	100
	0 8	5	36 6 ± 16 7	n s	22 4 ± 3 7	n s	20 2 ± 8 3	n s
	1 6	5	29 1 ± 7 1	n s	19 8 ± 7 7	n s	16 8 ± 5 8	69
	3 2	5	20 0 ± 12 0	52	11 0 ± 4 1	41	8 8 ± 3 5	36
	6 4	5	13 7 ± 7 2	35	6 3 ± 5 3	23	4 6 ± 3 7	19
$BaSO_4$III (+ 1 6 mM Na_2SO_4 per dose)	Controls	6	45 2 ± 9 7	100	38 7 ± 9 2	100	32 3 ± 11 3	100
	0 8	5	17 7 ± 14 6	39	6 5 ± 3 9	17	4 3 ± 2 7	13
	1 6	5	14 8 ± 8 8	33	3 9 ± 0 7	10	1 9 ± 0 6	6
	3 2	5	14 8 ± 11 4	33	3 8 ± 4 1	10	2 1 ± 0 8	7
	6 4	4	21 5 ± 7 4	48	4 3 ± 1 9	11	2 3 ± 1 5	7
Na_2SO_4 (+ 1 6 mM $BaSO_4$ III per dose)	Controls	5	35 5 ± 6 3	100	26 3 ± 6 7	100	19 5 ± 5 9	100
	0 8	5	16 0 ± 15 6	45	4 9 ± 3 0	18	2 3 ± 2 1	12
	1 6	5	14 0 ± 4 2	39	4 0 ± 1 2	15	1 4 ± 1 0	7
	3 2	5	45 5 ± 39 5	n s	6 9 ± 2 5	26	2 5 ± 1 4	13

[1] Content of ^{85}Sr in 1 femur times 20

[2] Arithmetic mean ± standard error of the mean multiplied by t value for 95% confidence level

[3] Difference not statistically significant

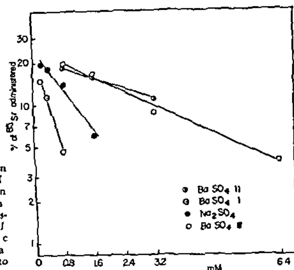


Fig 1 Skeletal retention of Sr in relation to the dose of sulphates administered Equations of regression lines were computed by using logarithms of percentage of Sr administered Points for various doses of sulphates therefore represent geometric means (i e arithmetic means of logarithms) Each point is based on five to six experimental values

and the animals were sacrificed 48 hours later In the first two experiments sodium sulphate was given in doses of 0 2 0 4 0 8 mM and 0 8 1 6 2 4, 3 2 mM in 2 ml and 3 ml respectively of distilled water In a further three experiments, various barium sulphates (VOLF & ROTH 1966) were tested 0 2 0 4 0 8 mM per dose of preparation I and 0 8 1 6 3 2 6 4 mM per dose of preparation II or III were administered in 2 ml and 3 ml of distilled water respectively Finally in two experiments increasing doses of barium sulphate (0 8 to 6 4 mM of preparation III per dose) each with 1 6 mM of sodium sulphate were administered as well as increasing doses of sodium sulphate (0 8 to 3 2 mM per dose) each with 1 6 mM of barium sulphate (preparation III)

In the study of the time factor 101 rats weighing from 180 to 200 g were used Sodium and barium sulphates (preparation I or preparation III) were administered alone or in combination (in doses of 0 8 mM or 1 6 mM each) at various intervals (from 0 to 80 min) after oral contamination with ^{85}Sr The animals were sacrificed 48 hours later Furthermore in an 8 day experiment 0 8 mM of each sulphate was given 10 min after the ^{85}Sr Whole body counting was carried out daily finally the ^{85}Sr content in the bones was also assessed

Results

The average skeletal retention of ^{85}Sr decreased significantly (by 40 % to 60 %) with sodium sulphate (Table 1) when at least 0 8 mM had been admin

Table 2

Effect of sulphates administered orally in doses of 0.8 mM at various time intervals after oral contamination with ^{85}Sr

Substances tested	Interval[1] (min)	Number of animals	Percentage of ^{85}Sr administered					
			Whole body				Skeleton[2]	
			After 24 hours		After 48 hours		After 48 hours	
			$\bar{x} \pm ts$[3]	Percentage of control	$\bar{x} \pm ts$	Percentage of control	$\bar{x} \pm ts$	Percentage of control
Na_2SO_4	Controls	6	42.1 ± 7.9	100	25.8 ± 5.3	100	27.0 ± 7.2	100
	0	5	37.8 ± 15.2	n.s.[4]	19.9 ± 7.9	n.s.	17.1 ± 5.2	63
	10	5	28.9 ± 7.6	69	16.4 ± 8.2	64	13.5 ± 6.4	50
	40	5	39.5 ± 14.0	n.s.	25.7 ± 2.9	n.s.	23.0 ± 6.9	n.s.
	80	5	52.5 ± 14.3	n.s.	31.8 ± 7.3	n.s.	32.8 ± 13.1	n.s.
$BaSO_4$ I	Controls	6	51.5 ± 25.7	100	31.6 ± 9.0	100	24.0 ± 7.6	100
	0	5	9.3 ± 6.8	18	5.2 ± 4.3	16	4.0 ± 3.4	17
	10	5	33.9 ± 23.9	n.s.	12.3 ± 3.0	39	7.8 ± 1.6	33
	40	5	25.8 ± 14.2	n.s.	13.9 ± 3.6	44	10.9 ± 2.2	45
	80	5	49.5 ± 32.3	n.s.	25.2 ± 11.2	n.s.	22.8 ± 12.5	n.s.
$BaSO_4$ III + Na_2SO_4	Controls	6	28.4 ± 9.8	100	24.7 ± 9.9	100	16.8 ± 6.1	100
	0	5	9.5 ± 9.2	33	3.7 ± 2.2	15	2.6 ± 1.9	15
	10	5	17.3 ± 11.3	61	9.6 ± 5.2	39	6.0 ± 4.1	36
	40	5	24.1 ± 9.7	n.s.	15.6 ± 6.3	n.s.	13.2 ± 6.6	n.s.
	80	5	30.5 ± 6.3	n.s.	26.2 ± 6.4	n.s.	19.5 ± 6.3	n.s.

[1] Time interval between administration of ^{85}Sr and sulphate
[2] Content of ^{85}Sr in 1 femur times 20
[3] Arithmetic mean ± standard error of the mean multiplied by t value for 95 % confidence level
[4] Difference not statistically significant

istered in comparison with the control group. The average effectiveness of doses up to 3.2 mM did not differ substantially, whereas doses lower than 0.8 mM were ineffective.

After the administration of barium sulphate (Table 1) the retention of ^{85}Sr decreased considerably with as low a dose as 0.2 mM of preparation I (by 38 %). Other barium sulphate preparations proved effective only when administered in higher doses. The average skeletal retention of ^{85}Sr decreased significantly in comparison with the control group after 6.4 mM of preparation II (by 49 %) and after 3.2 or 6.4 mM of preparation III (by 64 % or 81 % respectively).

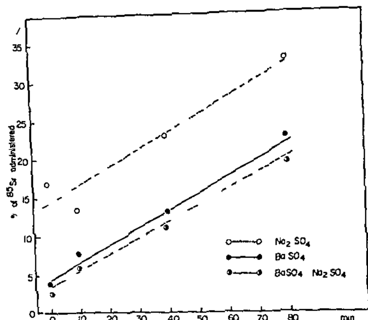


Fig 2 The skeletal retention of Sr in relation to the time interval between the administration of Sr and sulphates Each point represents the arithmetic mean of five to six experimental values

The decrease in skeletal retention of ⁸⁵Sr was exponentially related to the dose of both sulphates within the dose range from 0 2 to 1 6 mM of sodium sulphate and from 0 2 to 6 4 mM of barium sulphate When plotting the average experimental values obtained in the above experiments regression lines may be fitted on the semi logarithmic scale (Fig 1) Their equation apparently show indicative parameters for sections on the y axis which are very close together

$$y = 25.4\ e^{-0.855} \quad (1)$$
$$y = 23.2\ e^{-1.988} \quad (2)$$
$$y = 21.7\ e^{-0.19x} \quad (3)$$
$$y = 24.1\ e^{-0.291} \quad (4)$$

When extrapolating the regression lines towards lesser doses they practically converge on axis y to the point that indicates the average retention of ⁸⁵Sr in controls

It was found when gradually increasing the doses of barium sulphate (preparation III) administered in combination with a standard addition of sodium sulphate that a considerable improvement in the effectiveness of the

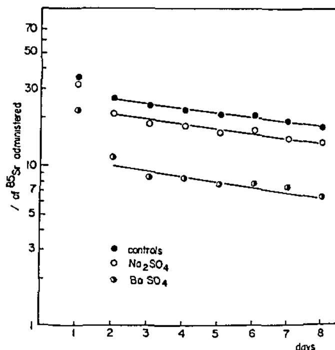


Fig. 3 Whole body retention of ^{85}Sr following a single dose of sulphates administered 10 min after oral contamination with radiostrontium. Each point represents the arithmetic mean of eight experimental values (in the sodium sulphate group of seven values).

barium sulphate (Table 1) was achieved. With 1.6 mM of both sulphates the average skeletal retention of ^{85}Sr decreased by 94 % in comparison with the control group; the doses seem to be optimal.

Increasing doses of sodium sulphate administered in combination with a standard addition of barium sulphate again produced best results with 1.6 mM of both sulphates. The average skeletal retention of ^{85}Sr decreased by 93 % in comparison with the control group.

The average effectiveness of sulphates and their combinations, within the ranges studied, decreased linearly with time from the ingestion of ^{85}Sr up to the start of the treatment (Table 2). Sodium and barium sulphates lost their effectiveness after 40 min and 80 min respectively. A combination of barium and sodium sulphates produced similar results. The average retention of ^{85}Sr in the control group was however unusually low and the relative decrease in ^{85}Sr retention was thus less marked.

Regression lines may be fitted to the experimental values indicating skeletal retention of ^{85}Sr in the above experiments. Their equations demonstrate very close line gradients:

$$y = 0.2249\,x + 14.30 \qquad (5)$$

$$y = 0.2220\,x + 4.17 \qquad (6)$$

$$y = 0.2085\,x + 3.54 \qquad (7)$$

Regression lines therefore are practically parallel and in accordance with the effectiveness of the agents at varied levels (Fig 2)

Data obtained with a single dose of sulphates administered 10 min after ⁸⁵Sr are presented in Fig 3 The observation period was prolonged The average whole body retention of ⁸⁵Sr was plotted on a semilogarithmic scale Regression lines may be fitted to the points (from the 2nd to the 8th day) they are at various levels but their gradients are practically equal in all three groups

$$y = 29.2\ e^{-0.065} \quad (8)$$
$$y = 22.9\ e^{-0.063} \quad (9)$$
$$y = 11.5\ e^{-0.074x} \quad (10)$$

After the administration of barium sulphate the retention of ⁸⁵Sr was from the second day to the end of the experiment significantly lower than in the control group (approximately by 60 %) Even though the average retention of ⁸⁵Sr after the administration of sodium sulphate was lower than in the control group the difference was not significant The result corresponded with the average skeletal retention of ⁸⁵Sr on the 8th day after administration in the group with barium sulphate it was significantly reduced (by 63 %) in comparison with controls

Discussion

An exponential relationship existed within a certain dose range between the dose of sodium and barium sulphates and their effect in vivo When increasing the amount of sodium sulphate above 1 6 mM per dose no further improvement was achieved whereas the effectiveness of barium sulphate (preparation III) increased up to the highest dose tested (6 4 mM) The effectiveness increased considerably when within this range sodium sulphate was added to each dose of barium sulphate The optimal effect was however obtained already with 1 6 mM of barium sulphate per dose as well as with increased sodium sulphate doses to which barium sulphate was added This could be expected when sulphates had been administered some time after the ⁸⁵Sr which in the meantime was partially absorbed and deposited in the tissues

MacDonald et coll (1955) described a similar relation of calcium and ⁸⁵Sr, when different amounts of calcium chloride mixed with a dose of beef slurry and Sr were administered orally to rats The fraction of the Sr dose that was found in the bone became smaller as the amount of accompanying calcium was raised but progressively larger and larger doses of *calcium were required* to maintain this trend

Ogawa et coll (1962) administered subcutaneously to mice varied doses of

magnesium chloride and magnesium sulphate These substances were ineffective on the excretion of ^{90}Sr when injected in a small dose but increased its excretion and decreased its retention in bone when administered in large doses

The possibility of reducing the intestinal absorption of radiostrontium depends on the time interval between its ingestion and the beginning of treatment Strontium is well absorbed, mainly from the small intestine (JONES & COID 1956, CRAMER & COLP 1959, MICHON & GUILLOUX 1959), most of the absorption occurring within the first 5 to 6 hours (JONES & COID, CRAMER 1959) It may be assumed therefore that the effectiveness of substances that prevent the absorption of radiostrontium from the gastrointestinal tract will decrease relatively rapidly with the time interval

According to COLP & GREENBERG (1944) magnesium sulphate had no effect as early as 10 min after the ingestion of radiostrontium MICHON & GUILLOUX (1959) observed a lower effect when ion exchangers were administered at 45 min after ^{90}Sr than when administered after 5 to 10 min RAZUMOVSKII et coll (1959) similarly observed a lower effectiveness of ion exchangers given one hour after ^{89}Sr

Intervals between the administration of ^{85}Sr and sulphates in the present experiments were chosen in order to cover the period during which the largest fraction of ^{85}Sr left the stomach (10 to 80 min after the oral contamination — unpublished result) At that time the sulphates also lost their effectiveness A similar result was published by BRUCE (1963) who administered calcium phosphate at various intervals after oral contamination with radiostrontium

A further increase in the effectiveness of barium sulphate by the addition of sodium sulphate was observed only in the shortest intervals (up to 10 min), when administering sulphates later after the contamination with ^{85}Sr this combination lost its effect as well

The decrease in the effectiveness of sulphates with time is linear within the range investigated and probably in connection with the intestinal passage of the radioisotope This presumption is also supported by the fact that regression lines for agents with varied effectiveness, although at different levels, are practically parallel

The high effectiveness of barium and sodium sulphates in combination when given immediately after radiostrontium contamination and its rapid decrease with time from the beginning of treatment means in practice that first aid has to be rendered as soon as possible

It seems however that a repetition of the treatment would be of little importance We could demonstrate, in an 8 day experiment that ^{85}Sr bound by the sulphate is not released later in this experiment the difference in reten

tion of ^{85}Sr between the control and the treated groups remained unchanged from the second to the eighth day after one single dose of sulphate The variance of values in the group with barium sulphate was much smaller during the whole experiment

It may be assumed that the relationship between the effectiveness of sulphates and time after ingestion of radiostrontium in man will be somewhat more favourable than in rats owing to a later removal of the ingesta from the stomach It also should be remembered that the volume of ingested radiostrontium will in most cases be smaller than in the present experiments in which the volume of ^{85}Sr solution (and the water used for rinsing) given to rats would correspond approximately to 250 ml of liquid in man Following inhalation the part of radioactivity retained in the respiratory tract gradually moves into the oral cavity and is swallowed Absorption of this fraction could be prevented even after longer periods of time

It may be expected therefore that first aid treatment with sulphates will be successful if started within several hours after ingestion and possibly later after inhalation of radiostrontium

Conclusion

The results of our experiments indicate that the diagnostic roentgen contrast medium Skiabaryum as well as sodium magnesium calcium and barium sulphates are effective means in minimizing the absorption of ^{85}Sr from the gastrointestinal tract in rats Their average effect did not differ significantly though it was better than the influence of strontium sulphate (VOLF & ROTH 1965)

The effect of sulphates was verified in repeated experimental series and under varying conditions Strontium 85 chloride was administered to male white rats in the experiments described This is in agreement with the previous investigations with Skiabaryum in female rats in which radiostrontium ^{89}Sr was administered once as chloride (VOLF 1960) and once as nitrate (VOLF 1961) The intestinal absorption of radiostrontium is prevented by Skiabaryum also in man (VOLF 1963)

Barium sulphate covers almost all the properties of the agents designed to reduce the intestinal absorption of radioactive substances as suggested by KROLL (1960) viz

(1) they must not be absorbed from the gastrointestinal tract

(2) they must have a strong affinity for strontium in the presence of high concentrations of calcium

(3) they must have a high ion exchange capacity for strontium per dose administered

(4) they must be non toxic, and

(5) they must not be metabolised or broken down chemically in the gastro intestinal tract

Effectiveness increases substantially if barium sulphate is combined with sodium or magnesium sulphates The treatment remains harmless though a certain fraction of sulphate ions is being absorbed Reduction in the skeletal ^{85}Sr retention by more than 90 %, in comparison with the controls, was repeatedly observed in the experiments when treatment started 10 min after oral contamination BALABUKHA & RAZUMOVSKII (1963) mentioned in their review that effective means can prevent the radioisotope retention in the skeleton by 40 % to 60 % when given shortly before or after the radiostrontium reached the stomach

A comparison of the effectiveness of sulphates and their combinations, and the influence of certain physiologic factors upon the effectiveness of treatment (VOLF & ROTH 1966) suggest that from a practical point of view it is desirable to look for the possibly most effective means and administer the drugs in sufficient doses The present work indicates that for these purposes it is possible to use barium sulphate or Skiabaryum combined with sodium or magnesium sulphates, which can be added as salts or in the form of a bitter mineral water Skiabaryum combined with sodium sulphate was significantly less effective in the experiments than a similar combination of barium and sodium sulphates (VOLF & ROTH 1965), on the other hand it is available in every roentgen department Sodium and magnesium sulphates are also common drugs and might be stored along with barium sulphate in first aid areas for use after accidental contamination with radioactive substances

The use of bitter mineral water has the advantage that the barium sulphate suspension can be prepared without any further trouble (the measuring and dissolving of the sulphate), it is well known and in common use, and no doubts exist as to its effects and harmlessness even in the hands of the inexperienced

Barium sulphate with the mineral water Zaječická (containing more magnesium than sodium sulphate) was substantially more effective in our experiments than a similar combination with the mineral water Šaratica (containing more sodium than magnesium sulphate)

Barium, sodium and magnesium sulphates would be useful for first aid treatment following internal contamination with radiostrontium and some other radioactive substances, especially the alkaline earth metals Since the time factor influences the effectiveness of the administered agent in a considerable degree, it is necessary to have everything ready to make it possible to render first aid directly at the site of the accident

Appendix (By Z ROTH)

Computing and testing of regression lines

When investigating the relation between the radiostrontium retention and the dose of sulphates percentages of the Sr dose retained in the skeleton were transformed to logarithms within the range of the sulphate doses including the zero-dose (i e without administration of sulphate) The logarithms of the Sr percentages in relation to the dose could be satisfactorily represented by a straight line Whether this change is statistically significant and the fitted line is satisfactory was tested by means of variance analysis Heteroscedascity did not occur so that the variance analysis could be used in these cases Both hypotheses mentioned were tested by the F test as shown in the table

Table

Analysis of variance

Source of variations	Sum of squares	D F	Ratio	F
Line regression	$S_L = \frac{\left[\sum_{1}^{k} n (x - x)(y - y)\right]^2}{\sum_{-1}^{k} (- x)}$	1	$s_L^2 = S_L$	$\frac{s_L^2}{s^2}$
Deviations from the linear regression	$S_L = S_D - S_L$	$k-2$	$s_L^2 = \frac{S}{k-2}$	$\frac{s_L^2}{s}$
In between the doses	$S_D = \sum_{1}^{k} (y - y)$	$k-1$		
Residual	$S_R = S_T - S_D$	$N - k$	$s = \frac{S_R}{N-k}$	
Total	$S_T = \sum_{-1}^{k} \sum_{j=1}^{n} (y_j - y)$	$N - 1$		

k indicates the number of doses n number of results for the i th group ($i = 1\ 2 \ldots k$) and $N = \sum_{1}^{k} n$ the total number of results y_j indicates the j th results (logarithm of the percentage of Sr dose for the i th group (dose of sulphates) y the average in the i th group y the total average x the dose in the i th group and $\bar{x} = \sum_{=1}^{k} n\ x / N$ the average of the dose in the whole experiment The equation of the fitted line is $y(x) = \bar{y} + b\ (x - \bar{x})$

where $b = \frac{\sum_{1}^{k} n\ (x - \bar{x})(\bar{y} - y)}{\sum_{1}^{k} n\ (x - x)}$

In the first line of the variance analysis the significance of the difference of the regression coefficient b from 0 was tested. The accordance of the fitted line with the experimental results was tested in the second line. If the computed value of the criterion F in the first line is higher than the critical value $F_{0.05}$ for 1 and $N-k$ degrees of freedom, the difference of the regression coefficient b from 0 is statistically significant on the significance level $p = 0.05$, and the dependence of the size of the average result in relation to the sulphate dose is proved. If the computed value of the criterion F in the second line is smaller than the critical value $F_{0.05}$ for $k-2$ and $N-k$ degrees of freedom, deviations from the fitted line are not significant and the line is assumed as satisfactory. The linear regression in evaluated cases was statistically significant although this was not the case when deviation from this regression was present. (The computed F was lower than 1 both for sodium and barium sulphates.)

The relation between the Sr retention and the time interval which passed from the contamination with Sr to the administration of sulphates was similarly evaluated: the linear relation was determined and no transformation was used. The variable y was the measured radioactivity and the variable x the time interval in minutes. A statistically significant linear regression of the activity in relation to the time interval was always present when computing the analysis of variance; deviations from this linear regression were statistically not significant. It may be concluded therefore that within the range of the time intervals investigated this dependence is approximately linear.

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SUMMARY

The significance of a great decrease in the skeletal retention of Sr after a single administration of optimal doses of barium and sodium sulphates is discussed. The difference in the retention between the treated and control groups did not change from the 2nd to the 8th day indicating that the treatment need not be repeated. All the agents were without effect when given 80 minutes after oral contamination with Sr.

ZUSAMMENFASSUNG

Die bedeutsame Verminderung der Aufspeicherung von Sr die nach Verabreichung einer optimalen Dosis von Barium und Natriumsulfat im Skelett auftritt wird besprochen. Es war kein Unterschied in der Aufspeicherung vom zweiten bis zum achten Tag zwischen den behandelten und den unbehandelten Fallen was beweist, dass man die Behandlung nicht zu wiederholen braucht. Alle Behandlungsmittel waren zwecklos, wenn man sie 80 Minuten nach der oralen Verbreichung des Sr gab.

RESUMÉ

Les auteurs examinent l intérêt d une diminution importante de la rétention osseuse de Sr apres une administration unique de doses optimales de sulfates de baryum et de sodium La difference de rétention entre le groupe traité et le groupe témoin ne change pas du 2 au 8 jour ce qui indique qu il est inutile de répéter le traitement Tous les agents pharmacodynamiques sont sans effet quand ils sont donnes 80 minutes après contamination orale par Sr

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In the first line of the variance analysis the significance of the difference of the regression coefficient b from 0 was tested. The accordance of the fitted line with the experimental results was tested in the second line. If the computed value of the criterion F in the first line is higher than the critical value $F_{0.05}$ for 1 and $N-k$ degrees of freedom, the difference of the regression coefficient b from 0 is statistically significant on the significance level $p = 0.05$ and the dependence of the size of the average result in relation to the sulphate dose is proved. If the computed value of the criterion F in the second line is smaller than the critical value $F_{0.05}$ for $k-2$ and $N-k$ degrees of freedom, deviations from the fitted line are not significant and the line is assumed as satisfactory. The linear regression in evaluated cases was statistically significant although this was not the case when deviation from this regression was present. (The computed F was lower than 1 both for sodium and barium sulphates.)

The relation between the ^{85}Sr retention and the time interval which passed from the contamination with Sr to the administration of sulphates was similarly evaluated: the linear relation was determined and no transformation was used. The variable y was the measured radioactivity and the variable x the time interval in minutes. A statistically significant linear regression of the activity in relation to the time interval was always present when computing the analysis of variance; deviations from this linear regression were statistically not significant. It may be concluded therefore that within the range of the time intervals investigated this dependence is approximately linear.

Acknowledgements

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SUMMARY

The significance of a great decrease in the skeletal retention of Sr after a single administration of optimal doses of barium and sodium sulphates is discussed. The difference in the retention between the treated and control groups did not change from the 2nd to the 8th day, indicating that the treatment need not be repeated. All the agents were without effect when given 80 minutes after oral contamination with ^{85}Sr.

ZUSAMMENFASSUNG

Die bedeutsame Verminderung der Aufspeicherung von Sr die nach Verabreichung einer optimalen Dosis von Barium- und Natriumsulfat im Skelett auftritt wird besprochen. Es war kein Unterschied in der Aufspeicherung vom zweiten bis zum achten Tag zwischen den behandelten und den unbehandelten Fällen, was beweist, dass man die Behandlung nicht zu wiederholen braucht. Alle Behandlungsmittel waren zwecklos, wenn man sie 80 Minuten nach der oralen Verabreichung des Sr gab.

Tabelle 1

Zahl der strahlenbehandelten Patienten nach Behandlungsgruppen und Tumortyp geordnet

Patientgruppe	A	B	C	D
Blockierung von der Art. pulm.	+	+	—	—
Atmung	100% O	Atmosph. Luft	100% O	Atmosph. Luft
Plattenepithelkarzinom	4	1	4	5
Adenokarzinom				1
Oatcell Karzinom		1	3	4
Zahl der Patienten	4	2	7	10

Wie THOMLINSON und GRAY (14) bei Untersuchung von humanem Lungengewebe feststellten, kommt es beim Lungenkarzinom in Vegetationen von über 180 μ Dicke immer zu zentralen Nekrosen, an deren Peripherie halb nekrotische Tumorzellen vegetieren. Eine Erhöhung des Sauerstoffgehaltes verbessert die Strahlenempfindlichkeit dieser Zellen und eröffnet der Strahlentherapie neue Möglichkeiten. Auf diese im Tierexperiment bewiesenen Umstände gründet sich die Strahlenbehandlung in einer Sauerstoff-Überdruckkammer (3) und bei intraarterieller Applikation von H_2O_2 (8).

Für das Lungengewebe bestehen noch weitere Möglichkeiten für eine Verbesserung des Sauerstoffmilieus. NORDENSTROM u. Mitarb. (9, 11) konnten nach Verschluss der Art. pulmonalis mit einem Ballonkatheter und Atmen reinen Sauerstoffs unter atmosphärischem Druck eine Erhöhung des Sauerstoffdruckes im venösen Blut peripher vom Verschluss feststellen.

Diese Technik wurde nun erstmalig im Rahmen einer Kurzzeitbestrahlung von Lungenkarzinomen angewandt, und deren Wirkung auf den Bestrahlungseffekt im Primärtumor wurde untersucht.

Material und Methoden. Vom 1. August 1963 bis 30. November 1964 wurden 23 Patienten mit inoperablen Lungenkarzinomen behandelt. Die Altersverteilung war:

Alter in Jahren	51—60	61—70	71—80
Zahl der Patienten	4	15	4

Alle Patienten waren Männer und Zigarettenraucher. In 14 Fällen lag ein Plattenepithelkarzinom, in 8 Fällen ein undifferenziertes kleinzelliges Karzinom („Oatcell") und in einem Fall ein Adenokarzinom vor (Tabelle 1). Neun Fälle waren inoperabel auf Grund von Metastasen, in den übrigen

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KURZZEITFRAKTIONIERUNG BEI BESTRAHLUNG VON LUNGENKARZINOMEN MIT KOBALT 60 BEI SIMULTANER SAUERSTOFFATMUNG UND TEMPORÄRER BLOCKIERUNG DER ARTERIA PULMONALIS

von

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Die Ergebnisse der Strahlenbehandlung beim Lungenkarzinom sind, unabhängig von der bei der Behandlung verwandten Strahlenqualität, schlecht (1). Nach einem Jahr leben im Durchschnitt nur noch 20 bis 30 % und nach 3 Jahren weniger als 5 % der behandelten Patienten. Dies beruht hauptsächlich darauf, dass es sich bei den strahlenbehandelten Lungenkarzinomen um relativ grosse, inoperable und oft metastasierende Tumoren handelt, bei denen die Behandlung des Primärtumors ohne Bedeutung für die Prognose des Patienten ist. Andererseits neigen diese zu über 50 % aus Plattenepithelkrebsen bestehenden Tumoren sehr zu Lokalrezidiven, wahrscheinlich auf Grund frühzeitiger hypoxämischer Nekrosen und der hierdurch bedingten geringeren Strahlenempfindlichkeit.

Bei der Redaktion am 14. September 1965 eingegangen.



Abb 3 Kontrolle der Grossenausdehnung des von der blockierten rechten Unt r und Mittellappen rterie versorgten Gebietes das in den rechten Vorhof injiz erte Kontra tmittel fullt nur die Gefasse der linken Lunge und des rechten Obe lappens

ebenso die Injektion von wasserloslichem Kontrastmittel 10 % Urografin® zum Aufblasen des Ballons Um zu kontrollieren ob die Blockade vollstandig ist werden 10 ml Kontrastmittel peripher vom Ballon injiziert (Abb 1)

Die Kontrolle kann auch mit einer zentralen Injektion des Kontrastmittels erfolgen (Abb 2) In diesem Falle benutzt man einen Cava Katheter und injiziert 1 ml Kontrastmittel pro kg Korpergewicht Auch die selektive Okklusion einer Lungenlappenarterie kann mit einer zentralen Kontrastmit telinjektion kontrolliert werden (Abb 3)

Der Katheter in der Vena cava wird sowohl fur Kontrastmittelinjektionen wie auch Dauertropfinfusionen verwendet

Bei besonderen Messungen des Sauerstoffdruckes wird zur Entnahme von peripherem arteriellen Blut ausserdem ein Katheter perkutan in die Art femoralis eingelegt

Klinische Untersuchungen Folgende Untersuchungen wurden bei jedem Pa tienten vor der Behandlung ausgefuhrt Lungen und Skelettrontgen (Becken und Thorax) Hb Hamatokrit Leukozyten Thrombozyten, Differential blutbild Blutzucker Papierelektrophorese, Serum Eisen Bilirubin Kreatinin Thymoltest alkalische Phosphatasen GOT GPT Blutungs und Koagula



Abb. 1. Plattenepithelkarzinom im rechten Oberlappen. Okklusion der Oberlappenarterie mit Ballonkatheter. Injektion von 10 ml Kontrastmittel peripher vom Ballon. Die peripheren Zweige der Oberlappenarterie sind teilweise durch den Tumor disloziert.



Abb. 2. Okklusion der linken Lungenarterie durch kontrastgefüllten Ballonkatheter; das in die rechte Herzkammer injizierte Kontrastmittel strömt zu den erweiterten Zweigen der rechten Lungenarterie; ein minimaler Teil des Kontrastmittels hat den Ballon passiert und füllt die sehr schmalen Gefässverzweigungen der linken Unterlappenarterie.

Fällen war eine Operation nicht möglich wegen schlechter Lungenfunktion infolge Emphysems. In allen Fällen war ein Karzinom histologisch oder zytologisch nachgewiesen, 9 mal durch transthorakale Aspirationsbiopsie des Primärtumors, 3 mal durch Mediastinoskopie und 11 mal durch Bronchoskopie.

Da vor der Untersuchung nicht bekannt war, wie lange ein Ballonkatheter in der Art. pulmonalis liegen konnte, ohne Risiko für Thrombose und Infektion, begrenzten wir die Behandlungszeit auf maximal 14 Tage. Für diese Art der Fraktionierung lagen für die Bestrahlung von Lungenkarzinomen keine Erfahrungen vor. Es wurden daher Kontrollgruppen von Patienten mit und ohne Blockierung der Art. pulmonalis sowie mit und ohne Sauerstoffatmung behandelt. In Tabelle 1 werden diese vier Gruppen getrennt aufgeführt.

Katheterisierung. Die Blockierung der Lungenarterien geschieht mit einem perkutan durch die Vena femoralis eingeführten Ballonkatheter (9, 10). Der Ballonkatheter hat 2 Kanäle. Der eine dient zum Aufblasen des Ballons, der andere endet mit seiner Öffnung peripher vom Ballon und dient zur Entnahme von Blutproben oder zur Injektion von Kontrastmitteln. Das Einführen der Katheter in die Lungenarterien geschieht unter Durchleuchtungskontrolle,

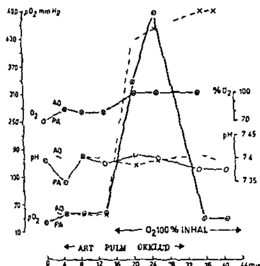


Abb 5 Deutliche Erhohung der Sauerstoffspannung (pO_2) und Sauerstoffsattigung (O_2) peripher von der Blockade in der A pulm wahrend der Atmung reinen Sauerstoffs unter atmospharischem Druck Keine signifikative Veranderung des pH Wertes im Lungenarterienblut AO = Aorta PA = Pulmonalarterie

Die Feldgrosse und der Einfallswinkel sowie die prozentuelle Strahlenbelastung per Feld variierte bei den einzelnen Patienten mit Hinsicht auf die Tumorlokalisation

Die Dosisberechnung erfolgte mit Korrektion fur schragen Einfall des Strahlenbundels auf die Korperoberflache (5) und fur den Luftgehalt der Lungen (13) Die kalkulierte Dosis im Zentralschnitt des gewahlten Behandlungsvolumens variierte um ± 5 % Bei der Planung der Behandlung wurde die gesunde Lunge nach Moglichkeit geschont das Mediastinum aber in einer Breite von 3 cm auf der dem Tumor gegenuberliegenden Seite mitbestrahlt

Tabelle 2

Grosse des Tumordurchmessers vor und nach der Strahlenbehandlung mit Okklusion der Lungenarterie und Sauerstoffatmung (Gruppe A) (Plattenepithelkarzinom)

Patient	Alter	Lokalisation	Vor Bestrahlung	Nach Bestrahlung	
			Tumordurchmesser in cm	Tumordurchmesser in cm	nach n Tagen gemessen
B E	72	li OI	3	1	16
O W	67	re OI	3	0 5	18
A E	69	re UI	3 5	0	14
H J	69	l UI	1	0 5	51

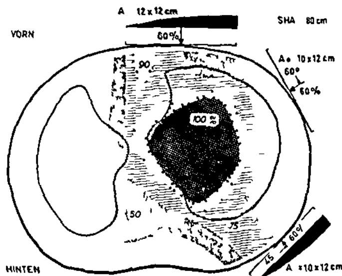


Abb. 4. Behandlungsplan mit Dosisverteilung für die Bestrahlung eines zentral belegenen Lungenkarzinoms mit Telecurie ^{60}Co. Dreifelderbestrahlung mit einem Keilfilterfeld vorn und hinten und einem offenen Feld von der Seite. Die Dosisverteilung wurde standardisiert zur Durchschnittsdosis im für die Bestrahlung gewünschten Volumen, wobei die Dosisbelastung per Feld 60 % beträgt.

tionszeit, Na, K, Ca, Cl im Serum, Spirometrie, EKG, Grundumsatz, Urinsediment, Albumin und Zucker im Urin.

Zweimal wöchentlich wurden Hb, Hämatokrit, Leukozyten, Thrombozyten, Koagulations- und Blutungszeit, sowie Protrombinindex und EKG, kontrolliert. Einmal wöchentlich fand eine Kontrolluntersuchung mit Papierelektrophorese, Leberfunktionsproben und Blutelektrolyten statt.

Die mit dem Ballonkatheter behandelten Patienten und ein Teil der Kontrollpatienten wurden während der Bestrahlung und der darauffolgenden 2 Wochen stationär aufgenommen. Nach der Behandlung wurde einmal im Monat eine Röntgenaufnahme der Lungen und ein Blutstatus angefertigt.

Alle Patienten erhielten während der Behandlung und der darauffolgenden 2 Wochen Antibiotika oder Sulfonamide. Alle Patienten der Gruppe A und B erhielten täglich als Dauertropfinfusion 3 ml einer 5 %igen Heparinlösung in 1 000 ml 5 %iger Glukoselösung.

Bei einem der ersten mit dem Ballonkatheter behandelten Patienten enstand eine lokale Thrombose in der Lungenarterie trotz Heparinbehandlung. Um diese Komplikation zu vermeiden, erhielten alle folgenden Patienten der Behandlungsgruppen A und B ausser Heparin täglich auch 500 ml einer Dextranlösung niedrigen Molekulargewichtes ∼ 40 000, Rheomacrodex® 10 % als Dauertropf.

Bestrahlung. Für alle Patienten wurde, mit Hilfe von Röntgenbildern, ein individueller Behandlungsplan angefertigt. Die Behandlung erfolgte auf 3 Stehfelder, ein vorderes und hinteres Keilfilter-Feld und ein offenes seitliches Feld (Abb. 4).



Abb 7 Ruckbildung eines Plattenepithelkarzinomes im rechten Unterlappen nach Bestrahlung mit simultaner Okklusion der rechten Unterlappenarterie und Atmung reinen Sauerstoffes vor Bestrahlung (a) und 14 Tage nach der Behandlung (b)

Technik auftreten werden in Abb 5 illustriert Nach Blockierung der Pulmonalarterie erhoht sich der Sauerstoffdruck massig Wenn der Patient dann zusatzlich reinen Sauerstoff atmet steigt der Sauerstoffdruck deutlich an in diesem Falle uber das achtfache des Wertes bei einfacher Blockade der Lungenarterie

Resultate

Lokale Veranderungen im Tumorgebiet nach der Bestrahlung Die geringe Zahl der *in dieser Untersuchung behandelten Falle lasst keine endgultige Beurteilung* der therapeutischen Moglichkeiten der hier beschriebenen Methode zu Es scheint jedoch bei der Strahlenbehandlung mit temporarer Blockierung der Lungenarterie und simultaner Sauerstoffbehandlung zu einem auffallend schnellen Ruckgang des Tumors zu kommen Diese Tumorverkleinerung konnte an Hand von Rontgenbildern *studiert werden wobei der Durch*messer des Tumors vor der Behandlung und zum Zeitpunkt der besten Ruckbildung nach der Strahlenbehandlung verglichen wurde Die Rontgenkontrollen geschahen zu Beginn mehrmals und spater mindestens einmal monatlich



a b

Abb 6 Plattenepithelkarzinom im rechten Oberlappen mit unscharfer peripherer Begrenzung und zentraler Einschmelzung (a) Verkleinerung des Tumors 18 Tage nach Bestrahlung mit simultaner Okklusion der rechten Oberlappenarterie und Atmung reinen Sauerstoffes (b)

Alle Patienten erhielten eine Gesamttumordosis von 4 500 rad wahrend 9 bis 14 Tagen Die Tagestumordosis betrug 500 rad Es wurden taglich alle drei Felder bestrahlt Die Feldgrosse variierte von 120 bis 180 cm² Die SHA betrug 80 cm

Nach Aufblasen des Ballons in der Art pulmonalis unter Durchleuchtungskontrolle atmete der Patient mindestens 10 Minuten vor Beginn und wahrend der Strahlenbehandlung reinen Sauerstoff unter atmospharischem Druck durch eine Nase und Mund bedeckende fest am Kopf fixierte Stoffmaske mit separatem Ausatmungsventil

Nach jeder Bestrahlung wurde der Ballon unter Durchleuchtungskontrolle entleert, blieb aber in der Art pulmonalis liegen

In einer fruheren Arbeit (11) konnte gezeigt werden, wie sich das Sauerstoffmilieu in der Lunge nach einfacher Blockierung eines Lungenarterienzweiges und in Kombination mit simultaner Atmung von reinem Sauerstoff verandert Die wichtigsten *Veranderungen die bei der Anwendung dieser*



Abb 7 Ru kbildung e nes Plattenepithelkarzinomes im rechten Unterl ppen nach Best ahlung mit s multaner Okklus on der rechten Unterlappenarterie und Atmung re nen Saue stoffes r Best ahl ng (a) und 14 Tage nach der Behandlung (b)

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Abb 8 Plattenepithelkarzinom im apikalen Segment des rechten Unterlappens Frontalbild (a) und Seitenbild (b) vor der Behandlung Nach fraktionierter Strahlenbehandlung verkleinerte sich der Tumor rasch Seitenbild (c) 37 Tage (d) 108 Tage nach Abschluss der Behandlung

Gruppe A Die oben beschriebene Verkleinerung des Tumors in dieser Behandlungsgruppe geht aus der Tabelle 2 hervor Zwei Falle mogen die Ruckbildung des Tumors in dieser Gruppe illustrieren

Ein Plattenepithelkarzinom im rechten Oberlappen bei einem 67 jährigen Mann mit langjahrigem mittelschweren Asthma bronchiale wird in Abb 6

Tabelle 3

[Gr]osse des Tumordurchmessers vor und nach der Strahlenbehandlung mit Okklusion der Lungenarterie und ohne Sauerstoffatmung (Gruppe B)

[Pat]ient	Alter	Tumortyp	Lokalisation	Vor Bestrahlung	Nach Bestrahlung	
				Tumordurchmesser in cm	Tumordurchmesser in cm	nach n Tagen gemessen
I S	68	O	re Ul	6	1 5	40
[?] K	59	P	re Ul	4	1 5	89

T[u]mortyp O = kleinzell ges undifferenziertes Karz nom P = Plattenepithelkarz nom

gezeigt Sechs bis sieben Monate vor der Krankenhausaufnahme hatte er Husten mit Blut tingiertem Sputum Die Lungenfunktionsprobe zeigte ein bedeutendes obstruktives Emphysem Bei der Rontgenuntersuchung fand man im rechten Oberlappen einen runden unscharf begrenzten Tumor mit zentraler Einschmelzung von 6 cm Durchmesser und vergrosserte Lymph knoten im oberen Teil des rechten Hilus Die Pleura uber dem Oberlappen war etwas verdickt und in beiden Lungen fand sich ein Emphysem Eine transthorakale Aspirationsbiopsie wurde vom Rucken her medial vom Schulterblatt vorgenommen Die mikroskopische Untersuchung des Zell

Tabelle 4

G[r]osse des Tumordurchmessers vor und nach der Strahlenbehandlung ohne Okklusion der Lungenarterie und mit Sauerstoffatmung (Gruppe C)

Patient	Alter	Tumortyp	Lokalisation	Vor Bestrahlung	Nach Bestrahlung	
				Tumordurchmesser in cm	Tumordurchmesser in cm	nach n Tagen gemessen
G L	70	P	re Ul	8	5	142
K H	58	P	li Ol Hilus reg	Nicht abgrenzbar	—	—
B F	55	O	li Ul	5	2	59
S E	67	P	li Ul	3	0	38
E T	71	O	li Ol	8	2	70
E R	65	O	li Ul	6 5	2 5	80
R J	63	P	re Ul	9	2	53

Tumortyp P = Plattenepithelkar nom O = kleinzell ges undifferenziertes Karz nom

Tabelle 5

Grosse des Tumordurchmessers vor und nach der Strahlenbehandlung ohne Okklusion der Lungenarterie und ohne Sauerstoffatmung (Gruppe D)

Patient	Alter	Tumortyp[1]	Lokalisation	Vor Bestrahlung	Nach Bestrahlung	
				Tumordurchmesser in cm	Tumordurchmesser in cm	nach n Tagen gemessen
N P	63	O	li Ul	7	5	47
F P	52	O	li Ul	8	5	115
E R	65	O	re Ol	4 5	2 5	3[illegible]
H C	69	P	li Ol	4	1 5	77
N I	65	A	li Ul	3	0 5	22
N R	63	O	li Ol	3 5	1 [illegible]	7
A L	72	I	re Ul	7	4	109
N H	65	P	li Ol	6	2	25
T L	77	P	re Ml	5	4 5	79
A K	63	I	li Ul	4 5	3 0	70

[1] Tumortyp P = Plattenepithelkarzinom O = kleinzelliges undifferenziertes Karzinom A = Adenokarzinom

materiales zeigte ein Plattenepithelkarzinom Die rechte Oberlappenarterie wurde mit einem Ballonkatheter blockiert und die Grosse des blockierten Lungenabschnittes durch Injektion einer kleinen Menge Kontrastflussigkeit kontrolliert (Siehe Abb 1)

In Abb 7 wird die Ruckbildung eines Plattenepithelkarzinoms im rechten Unterlappen eines 68 jahrigen Mannes demonstriert Bereits 14 Tage nach der Strahlenbehandlung war der Primartumor rontgenologisch nicht mehr feststellbar Nach 143 Tagen konnte man jedoch multiple kleine runde Infiltrate in der rechten Lunge feststellen Der Patient starb 6 Monate nach der Behandlung und bei der Sektion fand man multiple Metastasen in der rechten Lunge

Gruppe B Diese Gruppe besteht nur aus zwei Fallen Sowohl das 'Oatcell Karzinom wie auch das Plattenepithelkarzinom zeigten eine markante Verkleinerung nach der Strahlenbehandlung, die in dieser Gruppe mit Okklusion der Lungenarterie, doch ohne simultane Atmung von reinem Sauerstoff erfolgte (Tabelle 3)

Gruppe C Wie aus der Tabelle 4 hervorgeht fehlen einige Messwerte von Tumordiametern in Folge der Schwierigkeiten fur die Bestimmung der defi

Tabelle 6

Zahl der Patienten mit Allgemeinreaktion während und innerhalb eines Monates nach der Strahlenbehandlung in den verschiedenen Behandlungsgruppen

Reaktionen	Behandlungsgruppen			
	A	B	C	D
Hb 10 g	1	1	1	
Leukozyten 3 000/mm	2		2	
Thrombozyten 100 000 mm		1		
EKG	2	1	2	2
Thrombose in A. pulm	1			
Fieber 38 C	1			1
Singultus		1		

EKG = kurzzeitige ventrikulare und supraventrikulare Extrasystolen hämorrhagische Diathese

nitiven Tumorgrosse auf Grund von Atelektasen Sekundarinfektion und Ergussen Bemerkenswert ist dass bei einem Patienten ein vollstandiger Ruckgang des Tumors 38 Tage nach der Behandlung zu verzeichnen war

Gruppe D Aus der Tabelle 5 geht hervor dass sowohl Oatcell Karzinome wie auch Plattenepithelkarzinome und ein Adenokarzinom in dieser Gruppe vertreten sind *In allen Fallen konnte eine* Verkleinerung des Tumors beobachtet werden bei einem Oatcell Karzinom und bei dem einzigen behandelten Adenokarzinom trat diese uberraschend schnell ein

Allgemeine Symptome nach der Bestrahlung Die Kurzzeitbestrahlung mit Blockierung der Art pulmonalis und simultaner Sauerstoffatmung (Gruppe A) wurde *von allen Patienten trotz ihres hohen Alters und schlechten Allgemeinzustandes* gut vertragen Trotz eines relativ grossen bestrahlten Volumens das neben dem Primartumor noch 2/3 des Mediastinums umfasste kam es nur in wenigen Fallen zu Blutveranderungen (Tabelle 6) Ein Patient der Gruppe B entwickelte am letzten Tage der Bestrahlung eine hamorrhagische Diathese mit ausgedehnten Petechien am ganzen Korper Schleimhautblutungen und schwerer Thrombozytopenie die erst mit mehreren Bluttransfusionen behoben werden konnte Diese Komplikation ist jedoch fruher bei bedeutend kleineren Strahlendosen beobachtet worden und muss einer individuellen Überempfindlichkeit zugeschrieben werden Sie hat kausal nichts mit dem Typ der Kurzzeitbestrahlung zu tun

Die meisten Patienten klagten am Schluss der Behandlung uber Schluck

Tabelle 7

Überlebenszeit vom Abschluss der Bestrahlung bis zum 1 6 1965

Behandlungsgruppe	Patient	Tage	Verstorben	Lebend
A	B L	105	×	
	O W	292	×	
	V E	171	×	
	H J	45	×	
B	H S	102	×	
	O K	508	×	
C	G L	181	×	
	K H	462		×
	B I	142	×	
	S L	253	×	
	L T	426		×
	L R	114	×	
	R J	155	×	
D	N P	172	×	
	L P	283	×	
	L R	279	×	
	H C	349	×	
	N T	524		×
	N R	26	×	
	A L	408	×	
	N H	59	×	
	T L	90	×	
	V K	179		×

beschwerden infolge einer Strahlenreaktion in der Speiserohre Diese Beschwerden verschwanden spontan nach 2 bis 3 Wochen Sie sind ein Ausdruck fur die relativ hohe Strahlenempfindlichkeit der Ösophagusschleimhaut

Bei einem Patienten entwickelte sich ein hartnackiger Singultus, der eine Woche anhielt und therapeutisch sehr schwer zu beeinflussen war

Überlebenszeit Aus Tabelle 7 ist die Überlebenszeit vom Ende der Bestrahlung bis zum Abschluss der Beobachtungszeit ersichtlich Von den behandelten Patienten leben noch vier (ein Plattenepithelkarzinom und ein Oatcell Karzinom der Gruppe C sowie ein Plattenepithelkarzinom und ein Adeno karzinom der Gruppe D) Es besteht kein Unterschied zwischen den mittleren Überlebenszeiten der mit dem Ballonkatheter behandelten Patienten (236 Tage) und derjenigen der Kontrollfalle in den Gruppen C und D (241 Tage)

Tabelle 8

Histologischer Nachweis von Primartumor nach Bestrahlung (Sektionsbefund)

Behandlungsgruppe	Zahl der Patienten	Zahl der obduz Falle	Plattenepithelkarzinom		Adenokarzinom		Oatcell karzinom	
			+	−	+	−	+	−
A	4	2	1	1				
B	2	1	1					
C	7	4	1	1			2	
D	10	6	3				2	1

\+ *Tumorgewebe nachweisbar* — Kein Tumor nachweisbar

Histo zytologischer Nachweis von Primartumorzellen nach der Bestrahlung Zur zytologischen Kontrolle des Bestrahlungseffektes wurde die seit einiger Zeit entwickelte *transthorakale Aspirationsbiopsie unter* Durchleuchtungskontrolle angewandt Wenn nach der Bestrahlung in einem erneut wachsenden Tumor rezidiv mit der Aspirationsbiopsie viable Tumorzellen nachgewiesen werden konnten erhielten insgesamt 4 Patienten eine zusatzliche Bestrahlung Die verabfolgten Dosen variierten mit dem Allgemeinzustand des Patienten und der Lokalisation des Rezidives zwischen 2 000 bis 2 500 rad innerhalb 7 bis 10 Tagen Nach dieser Behandlung kam es zu bedeutenden Strahlenreaktionen im Zentrum des behandelten Volumens u a zur Einschmelzung von Lungengewebe im Bereich des Tumors bedeutender Fibrose Phrenikusparese und Pleuraexsudaten In zwei Fallen kam es zu umschriebenen Ösophagusnekrosen Pneumonie und Mediastinitis

In einem Teil der behandelten Falle war eine histologische Untersuchung des Primartumorgebietes nach dem Tode moglich In zwei Fallen von Plattenepithelkarzinomen (Gruppe A und C) und einem Fall von Oatcell Karzinom (Gruppe D) konnte kein Tumorrest mehr nachgewiesen werden (Tabelle 8) In einem Falle wurde ein grosser wandstandiger Thrombus in der Lungenarterie an der Okklusionstelle des Ballonkatheters gefunden In 8 der 13 obduzierten Falle lagen Metastasen des Knochenskelettes der parenchymatosen Organe und der abdominellen Lymphdrusen vor

Diskussion

Der Hauptzweck dieser Untersuchung war, zu prufen, ob die Okklusion der Lungenarterie mit einem Ballonkatheter bei simultaner Atmung von reinem Sauerstoff unter atmospharischem Druck bei der Bestrahlung von

Tabelle 7

Überlebenszeit vom Abschluss der Bestrahlung bis zum 1 6 1965

Behandlungsgruppe	Patient	Tage	Verstorben	Lebend
A	B E	105	×	
	O W	292	×	
	A L	171	×	
	H J	45	×	
B	H S	102	×	
	O K	508	×	
C	G L	181	×	
	K H	462		×
	B F	142	×	
	S E	253	×	
	E T	426		×
	E R	114	×	
	R J	135	×	
D	N P	172	×	
	E P	283		
	E R	279		
	H C	349	×	
	N I	524		×
	N R	26		
	A L	403		
	N H	59	×	
	T L	90		
	V K	179		×

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zuzulassen gleichgultig ob sie mit oder ohne Okklusion der Lungenarterie resp Atmung reinen Sauerstoffs durchgefuhrt wurde

Die gemessene Erhohung des Sauerstoffdruckes in der Lungenarterie die mit der hier beschriebenen Technik erreicht werden kann ist jedoch von einer Grossenordnung die eine Erhohung des Strahleneffektes vermuten lassen durfte

ZUSAMMENFASSUNG

Die Bestrahlung von Lungenkarzinomen wurde erstmalig mit einer simultanen intermittenten Okklusion der A pulmonalis und Atmung reinen Sauerstoffes unter atmospharischem Druck durchgefuhrt Die bereits fruher beschriebene Ballonkatheter Technik fuhrt zu einer Erhohung der Sauerstoffsattigung und moglicherweise gesteigerten Strahlenempfindlichkeit im Tumorbett Auf Grund der Katheter Technik wurde die Behandlungszeit auf 9 bis 14 Tage verkurzt und eine Tumordosis von 4 500 rad verabreicht Der Katheter lag maximal 15 Tage in der A pulmonalis Zur Thromboseprophylaxe wurde wahrend der Behandlung eine Heparin Glukose und Rheomacrodex Dauertropfinfusion gegeben Die Untersuchung hat gezeigt dass sowohl die intermittente Okklusion der Lungenarterie mit Sauerstoffatmung wie auch die Kurzzeitbestrahlung weit fortgeschrittener Lungenkarzinome praktisch durchfuhrbar ist

SUMMARY

Radiotherapy of bronchial carcinoma with simultaneous intermittent occlusion of the pulmonary artery and inhalation of oxygen at ordinary atmospheric pressure has been performed for the first time The application of a catheter with an inflatable cuff previously described results in higher oxygen saturation and possibly increased radiosensitivity in the tumour bed The catheter method enabled the period of treatment to be shortened to between 9 and 14 days the total tumour dose was 4 500 rad and the catheter remained in the pulmonary artery for a maximum period of 15 days A continuous drip of heparine glucose and rheomacrodex was employed to prevent thrombosis The investigation has demonstrated the feasibility of intermittent occlusion of the pulmonary artery during oxygen inhalation and of the short span radiotherapy of cases suffering from advanced bronchial carcinoma

RÉSUMÉ

Les auteurs ont pratiqué pour la première fois l irradiation de cancers du poumon avec occlusion simultanee intermittente de l artère pulmonaire et inhalation d oxygene pur a la pression atmospherique La technique de la sonde a ballonnet qui a déja été décrite entraine une élévation de la saturation en oxygene et peut-être une augmentation de la radiosensibilité du lit tumoral Cette technique de cathétérisme a permis de réduire le traitement à une duree de 9 à 14 jours et de délivrer une dose a la tumeur de 4 500 rad Le cathéter a été maintenu en place au maximum 15 jours dans l artère pulmonaire Pour prévenir la thrombose on a administré pendant le traitement une longue perfusion d héparine glucose et de rhéomacrodex Ce travail a prouvé qu on peut proceder pratiquement a l occlusion intermittente de l artère pulmonaire avec inhalation d oxygène ainsi qu au traitement court de cancers pulmonaires très avancés

Lungenkarzinomen praktisch durchführbar war. Durch die Erhöhung der Sauerstoffsättigung im Tumorbett, und wenn möglich im Tumor selbst, beabsichtigte man eine Steigerung der Strahlensensibilität. Ob es mit der angewandten Technik wirklich möglich war, die Sauerstoffsättigung in den Tumorzellen zu erhöhen, kann nicht beurteilt werden, solange keine zuverlässige Methode für eine intrazelluläre Messung des Sauerstoffdruckes im lebenden Patienten entwickelt ist.

Es wurde versucht, die Bestrahlungswirkung auf den Primärtumor durch Messungen des Tumordurchmessers im Röntgenbild vor und nach der Bestrahlung zu analysieren. Diese Messungen haben natürlich nur eine approximative Genauigkeit auf Grund der im Röntgenbild vorhandenen Schwierigkeiten zur genauen Abgrenzung des Tumors. Am lebenden Patienten sind sie jedoch eine Möglichkeit für die objektive Beurteilung der primären Strahlenwirkung auf den Primärtumor, ohne erneute Traumatisierung des Tumorgebietes, wie z. B. durch Bronchoskopie oder transthorakale Aspirationsbiopsie. Diese diagnostischen Eingriffe haben wir wegen der Blutungs- und Infektionsgefahr während der Strahlenreaktion 2 bis 3 Monate nach der Strahlenbehandlung möglichst vermieden.

Es konnte in dieser Untersuchung gezeigt werden, dass die Okklusion der Lungenarterie mit einem Ballonkatheter auch bei alten Patienten mit weit fortgeschrittenen Lungenkarzinomen bis zu 15 Tagen durchgeführt werden konnte. Soweit es sich beurteilen lässt, kann das Risiko einer Thrombose, die einmal in einer Lungenarterie auftritt, mit Hilfe von Heparin- und Rheomacrodex-Dauertropfinfusionen beherrscht werden. Auf Grund der angewandten Kathetertechnik war es notwendig, die Strahlenbehandlung in einem möglichst kurzen Zeitraume durchzuführen. Die von uns gewählte Bestrahlungszeit war 9 bis 14 Tage. Die während dieser Zeit verabfolgte Tumordosis war 4 500 rad. Sie kann strahlenbiologisch mit einer 6-wöchentlichen Fraktionierung von 6 000 rad verglichen werden.

Die Kurzzeitbestrahlung bietet gegenüber der längeren Fraktionierung gewisse Vorteile. Sie verkürzt eine evtl. notwendige stationäre Behandlung, verringert die Arbeitsbelastung einer Bestrahlungsabteilung und eignet sich besser für eine evtl. präoperative Bestrahlung. Wenn sie ohne Okklusion der Lungenarterie geschieht, kann sie in den meisten Fällen ohne Schwierigkeiten poliklinisch durchgeführt werden.

Bemerkenswert ist, dass trotz des relativ grossen bestrahlten Gewebevolumens und des notwendigerweise bestrahlten Blutvolumens keine stärkeren Reaktionen im Blutbilde auftraten.

Die Anzahl der in dieser Untersuchung behandelten Patienten ist zu klein, um sichere Schlüsse auf den Bestrahlungseffekt der Kurzzeitbestrahlung

Book reviews

COBALT 60 TELETHERAPY A HANDBOOK FOR THE RADIATION THERAPIST AND PHYSICIST By I H SMITH & J C M FETTERLY & J S LOTT et coll 464 pages, 25 figures and 0 tables Appendices A and B Hoeber Med Div Harper & Row New York 1964 Price 18 50 dollars

The authors of this book are the radiation therapists and physicists who in 1951 were the first in the world to begin using cobalt 60 teletherapy for cancer diseases at the London Clinic of the Ontario Cancer Treatment and Foundation in Canada The book is therefore of special interest The experiences from more than 10 years practical work are presented in a concise and readable form

An introductory section deals with the radiophysical and radiobiologic properties of cobalt 60 and the equipment used for various forms of telecobalt therapy The principles for dose planning and calculation as well as the methods for varying the dose distribution to suit different treatment techniques (moving beam therapy wedge filters) are also described Considerable space is given to variations in treatment techniques for different forms of tumor according to their anatomical location Suggestions for alternative treatments are illustrated with dose diagrams The tumor dose tissue reactions and complication risks are treated for each tumor group separately

A special section is devoted to radiation protection during the installation of a cobalt 60 teletherapy unit and to methods for checking output penumbra type of diaphragm and accessories A large number of technical tables such as depth dose percentage tables for stationary field and moving beam therapy are given in a special appendix

The book can be recommended as a concise handbook for physicians and physicists working with cobalt 60 teletherapy As the references are listed for each chapter it is also useful for teaching and research work

G Notter

NEUE ERGEBNISSE DER BIOPHYSIKALISCHEN FORSCHUNG Herausgeben vom Max Planck Institut fur Biophysik 166 Seiten Georg Thieme Verlag Stuttgart 1965 Preis 26 DM

The book was occasioned by the 25th anniversary of the Max Planck Institute of Biophysics Frankfurt/M A number of speeches given on that occasion are followed by a series of reports by eleven scientists of the institute on the various research programs under way These concern measurements of ambient radiation from natural sources and artificial radionuclides low level radioactivity measurements in human subjects dosimetry of high-energy radiations several aspects of biologic and chemical effects of radiation and microradiography

While by no means exhaustive — the space allotted to each paper ranges from 6 to 15 pages — most of the contributions seem to be of considerable value to those interested in the fields in question and testify to the high quality of research at the institute It is to be regretted that there has been a delay of three years in the publication There are however references to the literature of 1963 and 1964 so the papers seem to some extent to have been updated

Sten Benner

SCHRIFTTUM

1 BILLING U und LINHORN J Radiotherapy for carcinoma of the lung Acta radiol Ther Phys Biol 3 (1965) 281

2 BIERMAN H, KELLY K and SINGER G Studies on the blood supply of tumors in man IV The increased oxygen content of venous blood draining neoplasms J Nat Cancer Inst 12 (1952), 701

3 CHURCHILL DAVIDSON I, SANGER C, THOMLINSON R H High pressure oxygen and radiotherapy Lancet I (1955), 1091

4 — — — Oxygenation in radiotherapy II Clinical application Brit J Radiol 30 (1957) 406

5 DUTREIX A et DUTREIX J Construction des isodoses pour les surfaces obliques et irrégulières J Radiol Electrol 43 (1962) 671

6 GARLAND L H and SISSON M A Results of radiotherapy of bronchial cancer Radiology 67 (1956) 48

7 GUTTMAN R J Experiences in treatment of inoperable carcinoma of lung with 2 MeV and cobalt 60 irradiation Amer J Roentgenol 79 (1958) 505

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9 NORDENSTRÖM B Temporary unilateral occlusion of the pulmonary artery Acta radiol (1954) Suppl No 108

10 — Balloon catheters for percutaneous insertion into the vascular system Acta radiol 57 (1957) 411

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PROGRESS IN EXPERIMENTAL TUMOR RESEARCH Vol 6 Edit by F Homburger 340 pages 45 figures and 37 tables S Karger Basel 1965 Price 85 SFR/DM

Great emphasis is laid in the present volume of the series on recent advances made in studies concerned with the antigenicity of tumors Three of the six chapters of the volume deal with tumor viruses and virus induced neoplasms In the first written by J D ALMEIDA & A W HAM, the substructures of oncogenic virus particles are discussed The conclusion is drawn that these viruses fall into two fundamentally different groups one includes the nuclear DNA viruses with a simple cubic symmetry, and the other the cytoplasmic RNA viruses with a compound helical substructure Although the two types differ with regard to several distinct properties, it is pointed out that they nevertheless have certain similarities which indicate that the mechanism of inducing neoplastic transformation may be analogous

The specific tumor antigens of viral and non viral neoplasms are discussed in the chapters by H O SJOGREN & A AXELRAD The former considers the general principles of detecting tumor specific antigens and draws attention to the dangers of arriving at false conclusions if these principles are not strictly followed The difficulty of obtaining a critical proof of the existence of tumor specific antigens in human neoplasms is easily understood from the discussion on experimental tumors A list is presented indicating the neoplasms induced by chemical carcinogens by physical means or by oncogenic viruses which are doubtlessly characterized by specific antigenic properties An important difference between the antigenicity of viral and non viral tumors is that the latter have antigens specific for each individual tumor while the antigens of viral neoplasms are common to all tumors induced by the same virus The possibility of an integration of the virus with the cellular genome is discussed as an explanation of the development and maintenance of such antigenicity

In AXELRAD's chapter the recent investigations on the tumor specific antigens of Gross lymphoma and spontaneous lymphoma in AKR mice and which were performed by the recently developed spleen colony method are described Of special interest is the detailed discussion of the finding that AKR × C3H hybrid mice lack the ability to react immunologically against the specific antigens of Gross lymphoma This condition is suggested to explain why the Gross virus induces a high frequency of lymphoma in AKR mouse strain under natural conditions

The chapter by J F HENDERSON summarizes current literature on the effect of anticancer drugs on biochemical control mechanisms This indicates that the majority of purine and pyrimidine antimetabolites of significance in cancer chemotherapy can produce false feed back inhibition at one site or another No compound has been demonstrated unquestionably to inhibit tumor growth by interfering with biochemical control mechanisms The recent attempts to utilize drug combinations in order to potentiate the growth inhibiting effect are summed up in a chapter by A C SARTORELLI

The chapter by F J C ROE & M A Walters on some unsolved problems in lung cancer etiology is somewhat irrelevant as far as the rest of the book is concerned The authors highlight certain puzzling aspects of the disease such as its association with chronic bronchitis or certain bizarre pathologic syndromes Tobacco is considered to play a major role in the induction of lung cancer and several possible mechanisms are suggested

This volume of the series is like the previous ones a valuable source of information on the present position in different fields of experimental cancer research

L. Revesz